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(54) Title: METHOD FOR THE TREATMENT OR PREVENTION OF *FLAVIVIRUS* INFECTIONS USING NUCLEOSIDE ANALOGUES

(57) Abstract: The present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula (I) or a pharmaceutically acceptable salt thereof.

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METHOD FOR THE TREATMENT OR PREVENTION OF FLAVIVIRUS
INFECTIONS USING NUCLEOSIDE ANALOGUES

FIELD OF THE INVENTION

The present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues.

10 BACKGROUND OF THE INVENTION

Hepatitis is a disease occurring throughout the world. It is generally of viral nature, although there are other causes known. Viral hepatitis is by far the most common form of hepatitis. Nearly 750,000 Americans are affected by hepatitis each year, and out of those, more than 150,000 are infected with the hepatitis C virus (HCV).

20 HCV is a positive-stranded RNA virus belonging to the *Flaviviridae* family and has closest relationship to the pestiviruses that include hog cholera virus and bovine viral diarrhea virus (BVDV). HCV is believed to replicate through the production of a complementary negative-strand RNA template. Due to the lack of an efficient culture replication system for the virus, HCV particles were isolated from pooled human plasma and shown, by electron microscopy, to have a diameter of about 50-60 nm. The HCV genome is a single-stranded, positive-sense RNA of about 9,600 bp coding for a polyprotein of 3009-3030 amino-
30 acids, which is cleaved co- and post-translationally by cellular and two viral proteinases into mature viral proteins (core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). It is believed that the structural proteins, E1 and E2, the major glycoproteins are embedded into a viral lipid envelop and form stable heterodimers. It is also believed that the structural core protein interacts with

the viral RNA genome to form the nucleocapsid. The nonstructural proteins designated NS2 to NS5 include proteins with enzymatic functions involved in virus replication and protein processing including a polymerase, protease and helicase.

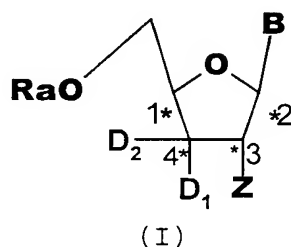
10 The main source of contamination with HCV is blood. The magnitude of the HCV infection as a health problem is illustrated by the prevalence among high-risk groups. For example, 60% to 90% of hemophiliacs and more than 80% of intravenous drug abusers in western countries are chronically infected with HCV. For intravenous drug abusers, the prevalence varies from about 28% to 70% depending on the population studied. The proportion of new HCV infections associated with post-transfusion has been markedly reduced lately due to advances in diagnostic tools used to screen blood donors.

20 The only treatment currently available for HCV infection is interferon- α (IFN- α). However, according to different clinical studies, only 70% of treated patients normalize alanine aminotransferase (ALT) levels in the serum and after discontinuation of IFN, 35% to 45% of these responders relapse. In general, only 20% to 25% of patients have long-term responses to IFN. Clinical studies have shown that combination treatment with IFN and ribavirin (RIBA) results in a superior clinical response than IFN alone. Different genotypes of HCV respond differently to IFN therapy, genotype 1b is more resistant
30 to IFN therapy than type 2 and 3.

There is therefore a great need for the further development of anti-viral agents.

Summary of the invention

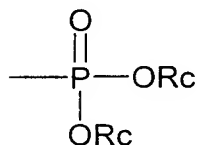
The present invention relates to a method for the treatment or prevention of *Flavivirus* infections in a host comprising administering a therapeutically effective amount of a compound having the formula I or a pharmaceutically acceptable salt thereof:



wherein

- 10 **B** is chosen from a purine, a pyrimidine or an analogue thereof;

Ra is chosen from H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, and



wherein each **Rc** are independently chosen from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl and an hydroxy protecting group; and

- Z** is halogen or **ORb**, wherein **Rb** is chosen from of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ acyl, or an hydroxy protecting group
- 20

D₁ and **D₂** are independently selected from N₃, F, or H, **D₁** and **D₂** can also be joined to be chosen from C₃-cycloalkyl, =CH₂, or =CF₂, and

wherein said compound is in the form of a single enantiomer or a mixture thereof including racemic mixtures;

with the proviso that when **B** is adenine, **Z** is **ORb**, **D₁** is H, **D₂** is H and **Rb** is H, **Ra** is not triphosphate or H.

In another aspect, there is provided a pharmaceutical formulation comprising the compounds of the invention in combination with a pharmaceutically acceptable carrier or excipient.

- 10 Still another aspect, there is provided a method for treating or preventing a viral infection in a host comprising administering a combination comprising at least one compound according to formula I and at least one further therapeutic agent.

In another aspect of the invention is the use of a compound according to formula I, for the preparation of a medicament for treating or preventing a viral infections in a host.

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DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the viral infection is chosen from *Flavivirus* infections.

In one embodiment, the *Flavivirus* infection is chosen from Hepatitis C virus (HCV), bovine viral diarrhea virus (BVDV), hog cholera virus and yellow fever virus.

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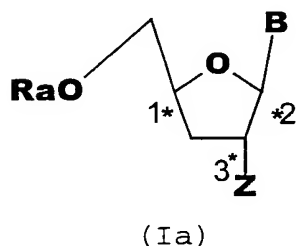
In an other embodiment, the *Flavivirus* infection is Hepatitis C virus.

In one embodiment, there is also provided a method for inhibiting or reducing the activity of viral polymerase

in a host comprising administering a therapeutically effective amount of a compound having the formula I.

In another embodiment, the viral polymerase is HCV polymerase.

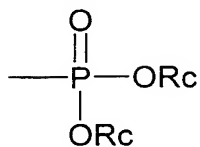
The present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ia or a pharmaceutically acceptable salt thereof:



wherein

B is chosen from a purine, a pyrimidine or an analogue thereof;

Ra is chosen from H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, and



wherein each **Rc** are independently chosen from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl and an hydroxy protecting group; and

Z is halogen or **ORb**, wherein **Rb** is chosen from of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ acyl, or an hydroxy protecting group; and

wherein said compound is in the form of a single enantiomer or a mixture thereof including racemic mixtures;

with the proviso that when **B** is adenine, **Z** is **ORb** and **Rb** is H, **Ra** is not triphosphate or H.

In one embodiment, the compounds and methods of the present invention comprise those wherein the following
10 embodiments are present, either independently or in combination.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 1-deaza-adenin-9-yl, 1-deaza-guanin-9-yl, 1-deaza-inosin-9-yl, 1-deaza-2-amino-purin-9-yl, 1-deaza-2-amino-6-chloro-purin-9-yl, 1-deaza-2-6-diamino-purin-9-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-
20 deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl, 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 2-aza-adenin-9-yl, 2-
30 aza-guanin-9-yl, 2-aza-inosin-9-yl, 2-aza-2-amino-purin-9-yl, 2-aza-2-amino-6-chloro-purin-9-yl, 2-aza-2-6-diamino-purin-9-yl, 3-deaza-thymin-1-yl, 3-deaza-cytosin-1-yl, 3-deaza-uracil-1-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl

each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymine-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl, 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 2-aza-adenin-9-yl, 2-aza-guanin-9-yl, 2-aza-inosin-9-yl, 2-aza-2-amino-purin-9-yl, 2-aza-2-amino-6-chloro-purin-9-yl, 2-aza-2-6-diamino-purin-9-yl, 3-deaza-thymine-1-yl, 3-deaza-cytosin-1-yl, 3-deaza-uracil-1-yl, 5-aza-thymine-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymine-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl

each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

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In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymine-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-

purin-9-yl, 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

In a further embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

In a further embodiment, **B** is chosen from guanin-9-yl, cytosin-1-yl, uracil-1-yl, each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6} alkyl or C_{1-6} acyl.

In a further embodiment, **B** is cytosin-1-yl, which is unsubstituted or substituted by at least one of NHR_3 , C_{1-6} alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6} alkyl or C_{1-6} acyl.

10 In a further embodiment, **B** is guanin-9-yl, which is unsubstituted or substituted by at least one of NHR_3 , C_{1-6} alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6} alkyl or C_{1-6} acyl.

In a further embodiment, **B** is uracil-1-yl, which is unsubstituted or substituted by at least one of NHR_3 , C_{1-6} alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6} alkyl or C_{1-6} acyl.

20 In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, 5-fluoro-cytosin-1-yl, uracil-1-yl, 5-fluorouracil or 1,2,4-triazole-3-carboxamide base (ribarivin base).

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, 5-fluoro-cytosin-1-yl, uracil-1-yl, or 1,2,4-triazole-3-carboxamide base (ribarivin base).

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In one embodiment, **B** is chosen from guanin-9-yl, cytosin-1-yl, 5'-fluoro-cytosin-1-yl, 5'-fluorouracil -1-yl or uracil-1-yl.

In one embodiment, **B** is chosen from guanin-9-yl, cytosin-1-yl, 5'-fluoro-cytosin-1-yl, 5'-fluorouracil -1-yl or uracil-1-yl.

In one embodiment, **B** is cytosin-1-yl.

In one embodiment, **B** is 5-fluoro-cytosin-1-yl.

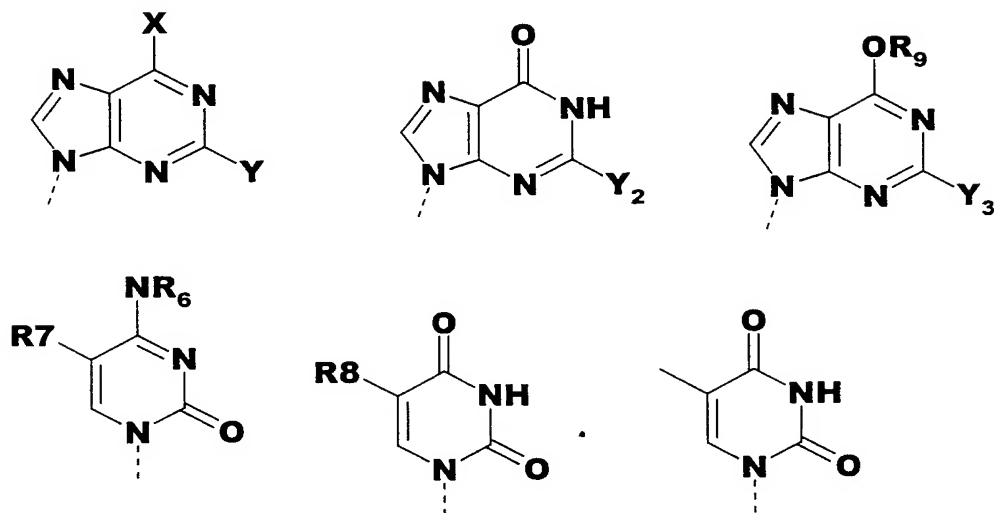
In one embodiment, **B** is 5-fluorouracil.

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In one embodiment, **B** is guanin-9-yl.

In one embodiment, **B** is uracil-1-yl.

In a further embodiment, **B** is



Wherein;

X is H, halogen or NHR₁₀, wherein **R₁₀** is H, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl;

Y is H, halogen or NHR₁₁, wherein **R₁₁** is H, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl;

Y₂ is H, halogen or NHR₁₂, wherein **R₁₂** is H, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl;

R₉ is H, hydroxy protecting group, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl;

Y₃ is H, halogen or NHR₁₃, wherein **R₁₃** is H, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl;

R₇ is H, halogen, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl;

R₈ is H, halogen, C₁₋₆acyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl.

10 In one embodiment,

X is H, halogen or NHR₁₀, wherein **R₁₀** is H.

Y is H, halogen or NHR₁₁, wherein **R₁₁** is H.

Y₂ is H, halogen or NHR₁₂, wherein **R₁₂** is H.

R₉ is H, hydroxy protecting group, C₁₋₆ alkyl.

Y₃ is H, halogen or NHR₁₃, wherein **R₁₃** is H.

R₇ is H, halogen, or C₁₋₆ alkyl.

R₈ is H, halogen or C₁₋₆ alkyl.

20 In a further embodiment,

X is H, F, or NHR₁₀, wherein **R₁₀** is H.

Y is H, F, or NHR₁₁, wherein **R₁₁** is H.

Y₂ is H, F, or NHR₁₂, wherein **R₁₂** is H.

R₉ is H.

Y₃ is H, F, or NHR₁₃, wherein **R₁₃** is H.

R₇ is H, F, or C₁₋₆ alkyl.

R₈ is H, F, or C₁₋₆ alkyl.

30 In one embodiment of the invention, **R_a** is chosen from H, monophosphate, diphosphate, and triphosphate.

In another embodiment of the invention, **R_a** is H.

In one embodiment, **Z** is F or **ORb**, wherein **Rb** is chosen from of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ acyl, or an hydroxy protecting group.

In one embodiment, **Z** is F.

In one embodiment, **Z** is **ORb**, wherein **Rb** is chosen from of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ acyl, or an hydroxy protecting group.

In one embodiment, **Z** is **ORb**, wherein **Rb** is chosen from of H, C₁₋₆ alkyl, or an hydroxy protecting group.

10 In one embodiment, **Z** is **ORb**, wherein **Rb** is chosen from of H, or methyl.

In one embodiment, **Z** is **ORb**, wherein **Rb** is H.

D₁ and **D₂** are independently selected from N₃, F, or H, **D₁** and **D₂** can also be joined to be chosen from cyclopropyl, difluorocyclopropyl --CH_2 , or --CF_2 .

D₁ and **D₂** are independently selected from F, or H, **D₁** and **D₂** can also be joined to be chosen from cyclopropyl, difluorocyclopropyl --CH_2 , or --CF_2 .

20 **D₁** and **D₂** are joined and are cyclopropyl.

D₁ and **D₂** are joined and are difluorocyclopropyl.

D₁ and **D₂** are joined and are --CH_2 .

D₁ and **D₂** are joined and are --CF_2 .

In one embodiment, **D₁** is H or F.

In one embodiment, **D₂** is H or F.

In one embodiment, **D₁** is H.

In one embodiment, **D₂** is H.

In one embodiment, **D₁** is F.

In one embodiment, **D₂** is F.

30 In one embodiment, **D₁** is N₃ and **D₂** is H.

In one embodiment, **D₁** is H and **D₂** is N₃.

In one embodiment, **D₁** is N₃ and **D₂** is F.

In one embodiment, **D₁** is F and **D₂** is N₃.

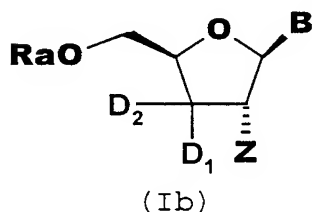
In one embodiment, **D₁** is H and **D₂** is F.

In one embodiment, D_1 is F and D_2 is H.

In one embodiment, D_1 and D_2 are H.

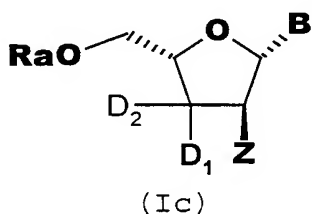
In one embodiment, D_1 and D_2 are F.

In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ib or a pharmaceutically acceptable salt thereof:



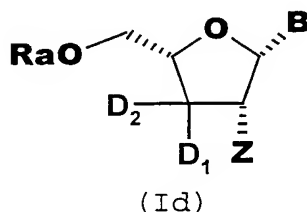
wherein Ra , B , D_1 , D_2 and Z are as defined above.

In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ic or a pharmaceutically acceptable salt thereof:



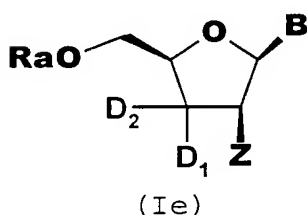
wherein Ra , B , D_1 , D_2 and Z are as defined above.

In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Id or a pharmaceutically acceptable salt thereof:



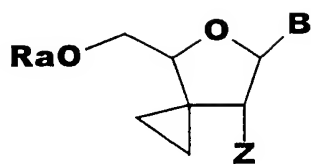
10 wherein **Ra**, **B**, **D₁**, **D₂** and **Z** are as defined above.

In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ie or a pharmaceutically acceptable salt thereof:



20 wherein **Ra**, **B**, **D₁**, **D₂** and **Z** are as defined above.

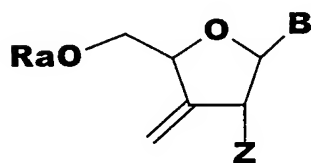
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula If or a pharmaceutically acceptable salt thereof:



(If)

wherein **Ra**, **B**, and **Z** are as defined above.

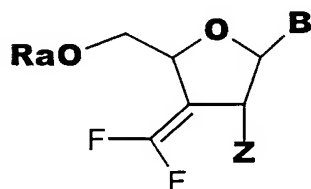
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ig or a pharmaceutically acceptable salt thereof:



(Ig)

wherein **Ra**, **B**, and **Z** are as defined above.

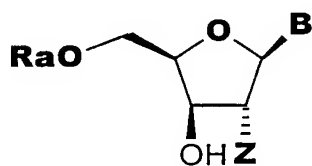
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ih or a pharmaceutically acceptable salt thereof:



(Ih)

wherein **Ra**, **B**, and **Z** are as defined above.

In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula **Ii** or a pharmaceutically acceptable salt thereof:



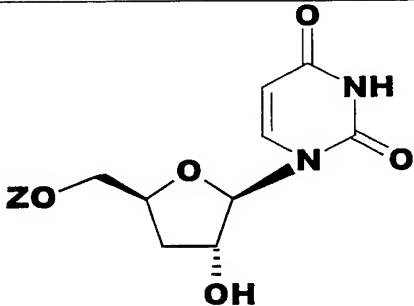
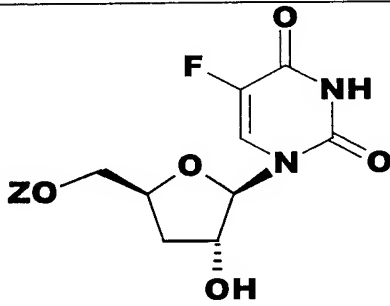
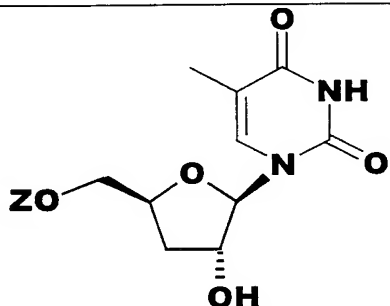
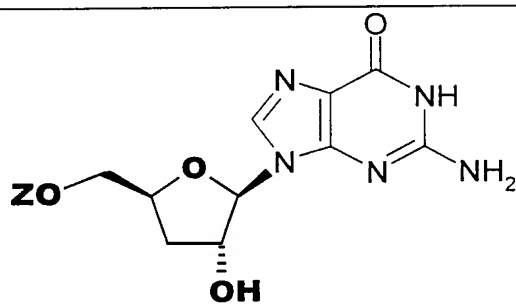
10

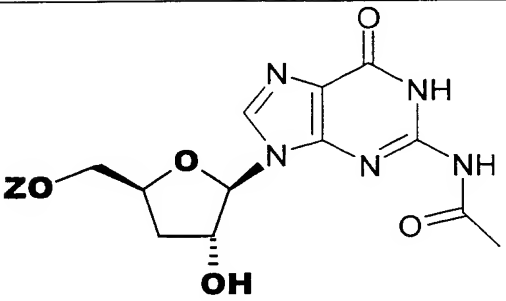
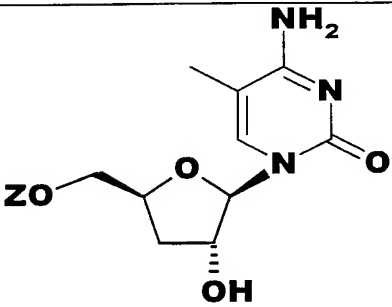
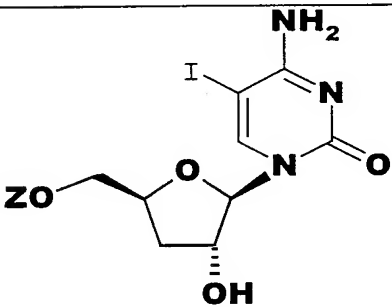
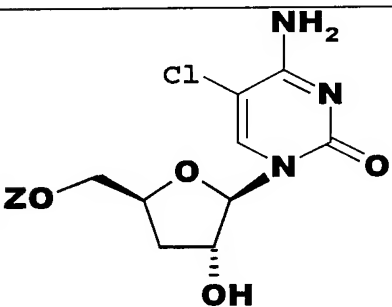
(Ii)

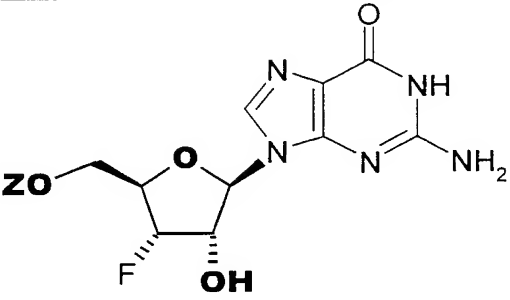
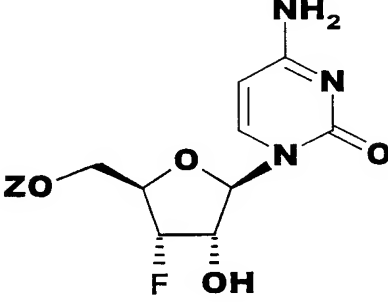
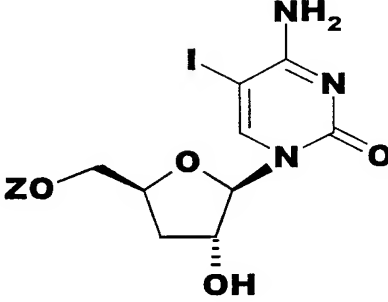
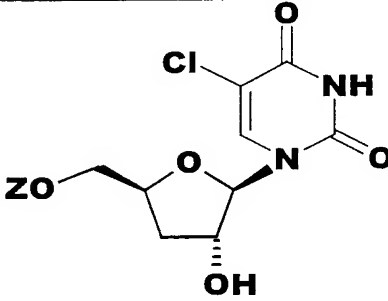
wherein **Ra**, **B**, and **Z** are as defined above.

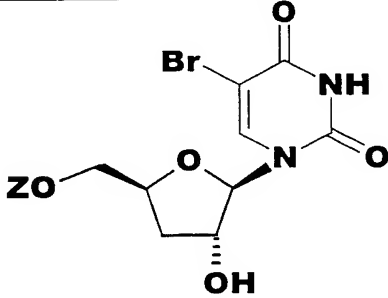
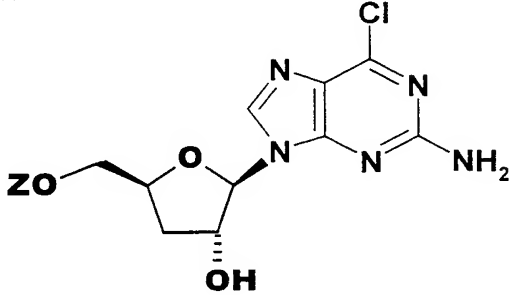
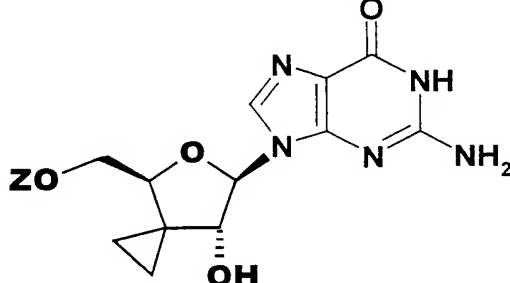
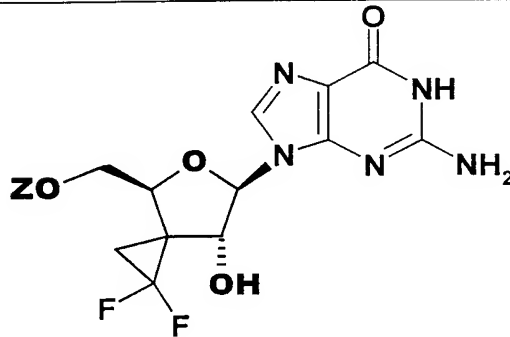
In one embodiment, a compound of formula (I) is chosen from:

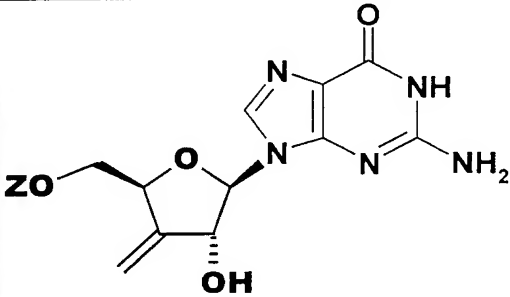
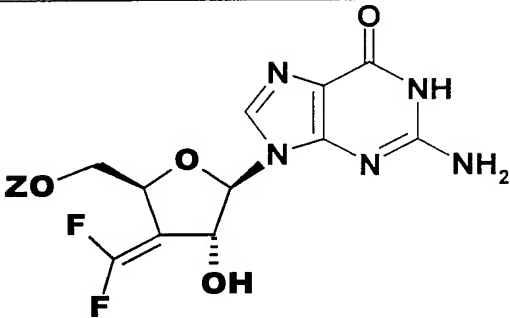
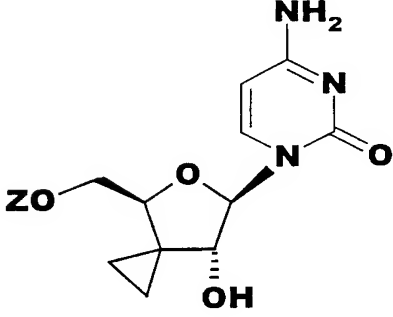
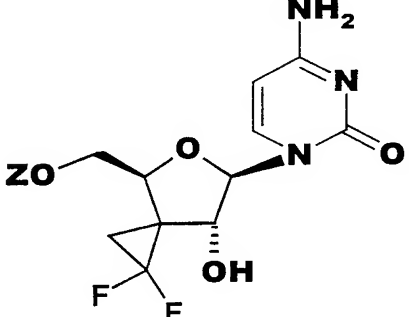
<p>3'-deoxycytidine Z=H, Compound #1,</p> <p>3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #2</p>	
<p>5-Fluoro-3'-deoxycytidine Z=H, Compound #3</p> <p>5-Fluoro-3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #4</p>	

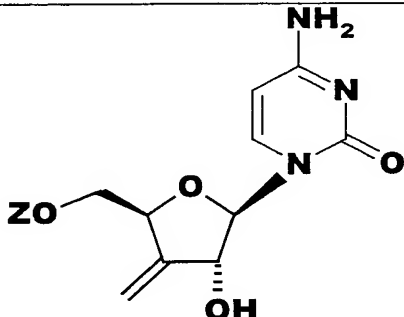
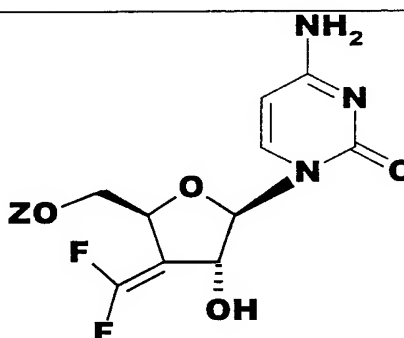
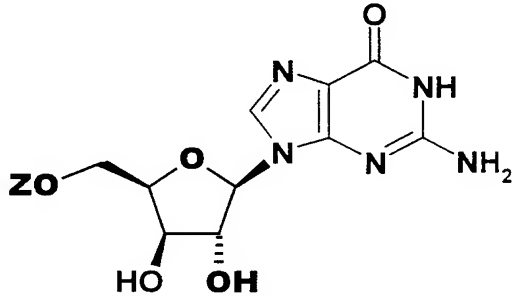
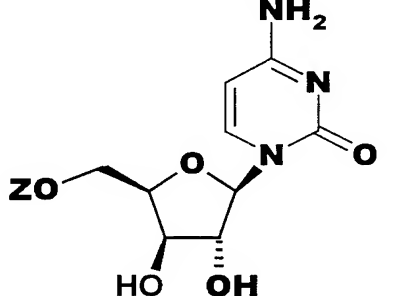
<p>3'-deoxyuridine Z=H, Compound #5</p> <p>3'-deoxyuridine- 5'triphosphate Z=triphosphate, Compound #6</p>	
<p>5-Fluoro-3'-deoxyuridine Z=H, Compound #7</p> <p>5-Fluoro-3'-deoxyuridine- 5'triphosphate Z=triphosphate, Compound #8</p>	
<p>3'-deoxythymidine Z=H, Compound #9</p> <p>3'-deoxythymidine- 5'triphosphate Z=triphosphate, Compound #10</p>	
<p>3'-deoxyguanosine Z=H, Compound #11</p> <p>3'-deoxyguanosine- 5'triphosphate Z=triphosphate, Compound #12</p>	

<p>2-N-acetyl-3'-deoxyguanosine Z=H, Compound #13</p> <p>2-N-acetyl-3'-deoxyguanosine- 5'triphosphate Z=triphosphate, Compound #14</p>	
<p>5-Methyl-3'-deoxycytidine Z=H, Compound #15,</p> <p>5-Methyl-3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #16</p>	
<p>5-Iodo-3'-deoxycytidine Z=H, Compound #17,</p> <p>5-Iodo-3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #18</p>	
<p>5-Chloro-3'-deoxycytidine Z=H, Compound #19,</p> <p>5-Chloro-3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #20</p>	

<p>3'-fluoro-3'-deoxyguanosine Z=H, Compound #21</p> <p>3'-fluoro-3'-deoxyguanosine - 5'triphosphate Z=triphosphate, Compound #22</p>	
<p>3'-fluoro 3'-deoxycytidine Z=H, Compound #23,</p> <p>3'-fluoro 3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #24</p>	
<p>5-Iodo-3'-deoxycytidine Z=H, Compound #25,</p> <p>5-Iodo-3'-deoxycytidine- 5'triphosphate Z=triphosphate, Compound #26</p>	
<p>5-Chloro -3'-deoxyuridine Z=H, Compound #27</p> <p>5-Chloro -3'-deoxyuridine- 5'triphosphate Z=triphosphate, Compound #28</p>	

<p>5-Bromo -3'-deoxyuridine Z=H, Compound #29</p> <p>5-Bromo -3'-deoxyuridine- 5'triphosphate Z=triphosphate, Compound #30</p>	
<p>6-Chloro-3'-deoxyguanosine Z=H, Compound #31</p> <p>6-Chloro -3'-deoxyguanosine - 5'triphosphate Z=triphosphate, Compound #32</p>	
<p>3'-spirocyclopropyl-3'- deoxyguanosine Z=H, Compound #33</p> <p>3'-spirocyclopropyl-3'- deoxyguanosine - 5'triphosphate Z=triphosphate, Compound #34</p>	
<p>3'-difluoro-spirocyclopropyl- 3'-deoxyguanosine Z=H, Compound #35</p> <p>3'- difluoro- spirocyclopropyl-3'- deoxyguanosine - 5'triphosphate Z=triphosphate, Compound #36</p>	

<p>3'-methylene-3'- deoxyguanosine Z=H, Compound #37</p> <p>3'-methylene-3'- deoxyguanosine - 5'triphosphate Z=triphosphate, Compound #38</p>	
<p>3'-difluoromethylene 3'- deoxyguanosine Z=H, Compound #39</p> <p>3'-difluoromethylene 3'- deoxyguanosine - 5'triphosphate Z=triphosphate, Compound #40</p>	
<p>3'-spirocyclopropyl-3'- deoxycytidine Z=H, Compound #41</p> <p>3'-spirocyclopropyl-3'- deoxycytidine -5'triphosphate Z=triphosphate, Compound #42</p>	
<p>3'-difluoro-spirocyclopropyl- 3'- deoxycytidine Z=H, Compound #43</p> <p>3'- difluoro- spirocyclopropyl-3'-</p>	

deoxycytidine -5'triphosphate Z=triphosphate, Compound #44	
3'-methylene-3'- deoxycytidine Z=H, Compound #45 3'-methylene-3'- deoxycytidine -5'triphosphate Z=triphosphate, Compound #46	
3'-difluoromethylene 3'- deoxycytidine Z=H, Compound #47 3'-difluoromethylene 3'- deoxycytidine -5'triphosphate Z=triphosphate, Compound #48	
9-β-D-xylofuranosyl-guanosine Z=H, Compound #49 9-β-D-xylofuranosyl-guanosine -5'triphosphate Z=triphosphate, Compound #50	
9-β-D-xylofuranosyl-cytidine Z=H, Compound #51 9-β-D-xylofuranosyl-cytidine -5'triphosphate Z=triphosphate, Compound #52	

<p>3'-azido-3'- deoxycytidine Z=H, Compound #53</p> <p>3'-azido-3'- deoxycytidine 5'triphosphate Z=triphosphate, Compound #54</p>	
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It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least three chiral centres and which are marked by 1, 2 and 3. When D1 and D2 are different, the compounds of formula (I) contain at least four chiral centres which are marked by 1, 2, 3 and 4. The compounds of formula (I) thus exist in the form of different optical isomers (e.g β -L and β -D) and geometric isomers trans or α and cis or β . All such enantiomers, geometric isomers and mixtures thereof including racemic mixtures are included within the scope of the invention. The single optical isomer or enantiomer can be obtained by method well known in the art, such as chiral HPLC, enzymatic resolution and the use of chiral auxiliary.

According to one embodiment, the atoms marked by 1 and 2 are in the cis or β configuration.

20 According to one embodiment, the atoms marked by 1 and 2 are in the cis or β configuration while the atom marked by 3 is in a trans or α configuration with respect to the atom 1 and 2.

According to one embodiment, compounds of formula I of the present invention are provided substantially in the form of the β -D configuration.

According to one embodiment, compounds of formula I of the present invention are provided substantially in the form of the β -L configuration.

By "substantially" is meant that there is more one enantiomer than of the other enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 95% free of the
10 corresponding β -D enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 97% free of the corresponding β -D enantiomer.

Still in another embodiment, the compounds of formula I of the present invention are at least 99% free of the corresponding β -D enantiomer.

20 In another embodiment, the compounds of formula I of the present invention are at least 95% free of the corresponding β -L enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 97% free of the corresponding β -L enantiomer.

Still in another embodiment, the compounds of formula I of the present invention are at least 99% free of the
30 corresponding β -L enantiomer.

There is also provided pharmaceutically acceptable salts of the compounds of formula I of the present invention. By the term pharmaceutically acceptable salts of the compounds of formula (I) are meant those derived from

pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids.

- 10 Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4^+ (where R is C_{1-4} alkyl) salts.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

- 20 In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

As used in the present application, "compound(s) of formula (I)" refers to all compounds identified by formula (I) and formulae (Ia) to (Ii).

- 30 As used in this application, the term "purine or pyrimidine or an analogue thereof" is meant a purine or pyrimidine base found in nucleotide or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the normal bases but may possess additional or lack certain of the functional properties of the normal bases. Such analogues include those derived by replacement of a

CH moiety by a nitrogen atom (for example, 5-azapyrimidines such as 5-azacytosine) or vice versa (for example 7-deazapurines, such as 7-deazadenosine or 7-deazaguanosine) or both (e.g. 7-deaza, 8-azapurines). Analogues of such bases also include those compounds wherein ring substituents are either incorporated, removed or modified by conventional substituents known in the art e.g. halogen, hydroxyl, amino, C1-6 alkyl. Such purine or pyrimidine base, analogues and derivatives will
10 be well known to those skilled in the art.

As used in this application, the term "alkyl" represents an unsubstituted or substituted (by a halogen, nitro, CONH₂, COOH, O-C₁₋₆ alkyl, O-C₂₋₆ alkenyl, O-C₂₋₆ alkynyl, hydroxyl, amino, or COOQ, wherein Q is C₁₋₆ alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl) straight chain, branched chain or cyclic hydrocarbon moiety (e.g. isopropyl, ethyl, fluorohexyl or cyclopropyl). The term alkyl is also meant to include alkyls in which one or more hydrogen atoms is
20 replaced by an halogen, more preferably, the halogen is fluoro (e.g. CF₃- or CF₃CH₂-).

As used in this application, the term "cycloalkyl" represents an "alkyl" as defined above which forms a ring.

The terms "alkenyl" and "alkynyl" represent an alkyl containing at least one unsaturated group (e.g. allyl).

30 The term "hydroxy protecting group" is well known in the field of organic chemistry. Such protecting groups may be found in T. Greene, Protective Groups In Organic Synthesis, (John Wiley & Sons, 1981). Example of hydroxy protecting groups include but are not limited to acetyl-2-thioethyl ester, pivaloyloxymethyl ester and isopropylloxycarbonyloxymethyl ester.

The term "aryl" represents an unsaturated carbocyclic moiety, optionally mono- or di-substituted with OH, SH, amino, halogen or C₁₋₆ alkyl.

The term "heteroaryl" represents an aryl wherein at least one carbon ring atom is substituted by a heteroatom (e.g. N, O, or S).

10 The term "aminoalkyl" represents an alkyl which is covalently bonded to the adjacent atom through a nitrogen atom.

The term "thioalkyl" represents an alkyl which is covalently bonded to the adjacent atom through a sulfur atom.

The term "alkoxy" represents an alkyl which is covalently bonded to the adjacent atom through an oxygen atom.

20 Halogen are chosen from F, Cl, I, and Br.

The term "host" represents any mammals including humans.

In one embodiment, the host is human.

The compounds of the present invention are can be prepared by methods well known in the art. For example, such methods are described in the following references
30 *J.Med.Chem.* **1991**, 34, 693-701; *Chem. Pharm. Bull.* **1995**, 43(11) 2005-2009; *J.Org.Chem.* **1989**, 54, 631-635; *Can.J.Chem.* **1975**, 53(19), 2975-2977; *Nucleosides Nucleotides*, **1990**, 9(8), 1045-60 and *Chemistry of Nucleosides and Nucleotides* edited by Leroy B.Towsend, 1988 Plenum Press Volumes 1 and 2; *Synthesis of 2'- β -fluoro- and 3'- β -fluoro-substituted guanine nucleosides.*

Effect of sugar conformational shifts on nucleophilic displacement of the 2'-hydroxy and 3'-hydroxy group with DAST. J. Org. Chem. , 57(26), (1992) 7315-21. Synthesis and antiviral and cytostatic properties of 3'-deoxy-3'-fluoro- and 2'-azido-3'-fluoro-2',3'-dideoxy-D-ribofuranosides of natural heterocyclic bases. J. Med. Chem. , 34(7), (1991) 2195-202. Synthesis of 9-(3-deoxy-3-fluoro- β -D-ribofuranosyl)guanine, a new potent antiviral agent. J. Chem. Soc., Chem. Commun. (1989) 10 (1989), (14), 955-7. Synthesis and antiviral activity evaluation of 3'-fluoro-3'-deoxyribonucleosides: broad-spectrum antiviral activity of 3'-fluoro-3'-deoxyadenosine. Antiviral Res. (1989), 12(3), 133-50. 3'-Fluoro-3'-deoxyribonucleoside 5'-triphosphates: synthesis and use as terminators of RNA biosynthesis. FEBS Lett. (1989), 250(2), 139-41. Reaction of 1-(2',3'-epoxy- β -D-lyxofuranosyl)uracil with hydrogen fluoride. The unexpected formation of 1-(3'-fluoro-3'-deoxy- β -D-ribofuranosyl)uracil. J. Heterocycl. Chem. (1984), 21(3), 20 773-5. Synthesis of 3'-deoxy-3'-fluorouridine. J. Carbohydr., Nucleosides, Nucleotides (1975), 2(3), 191-5. Synthesis of the 2'-deoxy-2'-fluoro and 3'-deoxy-3'-fluoro analogs of 8-bromoadenosine. Nucleic Acids Symp. Ser. (1997), 37(Symposium on Nucleic Acids Chemistry, 1997), 17-18. Synthesis of 8-substituted analogs of 3'-deoxy-3'-fluoroadenosine. Nucleosides Nucleotides (1998), 17(1-3), 115-122. A new synthesis of 3'-fluoro-3'-deoxyadenosine. Nucleosides Nucleotides (1991), 10(1-3), 719-21. Synthesis of 3'-fluoro-3'-deoxyadenosine starting 30 from adenosine. Synthesis (1990), (10), 900-5. Synthesis of 3'-deoxy-3'-fluoroadenosine by chemical transglycosidation. Z. Chem. (1989), 29(6), 209-10. Stereoselective synthesis of 3'-deoxy-3'-fluoroadenosine. Bull. Chem. Soc. Jpn. (1989), 62(6), 2119-20. Synthesis of nucleosides fluorinated in the sugar moiety. The

- application of diethylaminosulfur trifluoride to the synthesis of fluorinated nucleosides. Nucleosides Nucleotides (1989), 8(1), 65-96. Preparation of difluorouridines as antitumor agents. Efficient removal of sugar O-tosyl groups and heterocycle halogens from purine nucleosides with sodium naphthalenide. Tetrahedron (1997), 53(18), 6295-6302. Synthesis of fluoro and azido derivatives of purine nucleosides from nucleoside 2',3'-cyclic sulfates. Bioorg. Khim. (1994), 20(11), 1226-30.
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10 According to one embodiment, it will be appreciated that the amount of a compound of formula I of the present invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition for which treatment is required and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.01 to about 750 mg/kg of body weight per day, preferably in the range of 0.5 to 60 mg/kg/day, most preferably in the range of 1 to 20 mg/kg/day.

20

The desired dose according to one embodiment is conveniently presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

In another embodiment, the compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit
30 dosage form.

According to another embodiment of the present invention, the active ingredient is administered to achieve peak plasma concentrations of the active compound of from about 1 to about 75 μ M, preferably about 2 to 50 μ M, most preferably about 3 to about 30 μ M. This may be achieved,

for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to about 500 mg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

- 10 While it is possible that, for use in therapy, a compound of formula I of the present invention may be administered as the raw chemical, it is preferable according to one embodiment of the invention, to present the active ingredient as a pharmaceutical formulation. The embodiment of the invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic
- 20 and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

- According to one embodiment of the present invention, pharmaceutical formulations include but are not limited to those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and
- 30 intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods according to this embodiment include the step of bringing into association the active compound with liquid

carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

According to another embodiment, pharmaceutical formulation suitable for oral administration are conveniently presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a
10 powder or granules. In another embodiment, the formulation is presented as a solution, a suspension or as an emulsion. Still in another embodiment, the active ingredient is presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions,
20 emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds of formula I according to an embodiment of the present invention are formulated for parenteral administration (e.g. by injection, for example bolus
30 injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing an/or dispersing agents.

Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds of formula I, according to one embodiment of the present invention, are formulated as ointments, 10 creams or lotions, or as a transdermal patch. Such transdermal patches may contain penetration enhancers such as linalool, carvacrol, thymol, citral, menthol and t-anethole. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

20

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

30

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid. In another embodiment, they are presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

According to one embodiment, the formulations suitable for vaginal administration are presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds, in one embodiment of the invention, are used as a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or non-aqueous base also comprising one more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation the compounds, according to one embodiment of the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. In another embodiment, pressurized packs comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In another embodiment, the dosage unit in the pressurized aerosol is determined by providing a valve to deliver a metered amount.

Alternatively, in another embodiment, for administration by inhalation or insufflation, the compounds of formula I according to the present invention are in the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. In another embodiment, the powder composition is presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

In one embodiment, the above described formulations are adapted to give sustained release of the active ingredient.

The compounds of the invention may also be used in combination with other antiviral agents.

10 In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from protease inhibitors, polymerase inhibitors, and helicase inhibitors.

As used in this application, the term "interferon" include: interferon like molecules such as interferon (IFN), interferon α -2a, interferon α -2b, consensus interferon (CIFN) and other types of interferons.

20 In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from interferon (IFN), interferon α -2a, interferon α -2b, consensus interferon (CIFN), ribavirin, amantadine, rimantadine, interleukine-12, ursodeoxycholic acid (UDCA), glycyrrhizin and silybum marianum.

In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from Interferon- α , Ribavirin and Amantadine.

30 In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from Interferon- α and Ribavirin (REBETRON).

In one embodiment, the compounds of the invention may be employed together Interferon- α .

In one embodiment, the compounds of the invention may be employed together with Ribavirin.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

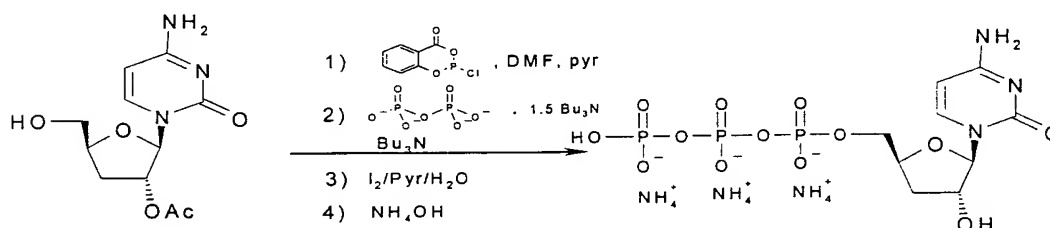
The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compound (I) or a pharmaceutically acceptable salts thereof is used in combination with a second therapeutic agent active against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone.

Appropriate doses will be readily appreciated by those skilled in the art.

The following examples are provided to illustrate various embodiments of the present invention and shall not be considered as limiting in scope.

Example 1. Preparation of 3'-DEOXYCYTIDINE 5'-
TRIPHOSPHATE TRIAMMONIUM SALT (Compound #2)



Procedure: To a stirring suspension of 3'-deoxy-2'-acetoxycytidine (15.0 mg, 0.056 mmol) in dry DMF (0.60 ml) was added dry pyridine (0.20 ml) followed by a freshly prepared solution of 2-chloro-4 H-1,3,2-benzodioxaphosphorin-4-one 0.5 M in 1,4-dioxane (111 μ l, 0.056 mmol). The mixture was stirred 30 minutes at room temperature, then tributylamine (36 μ l, 0.152 mmol) and a solution of tributylammonium pyrophosphate 0.5 M in DMF (101 μ l, 0.051 mmol) were added simultaneously. The
10 mixture was stirred another 30 minutes. A solution of I2 1% in pyridine/H2O (98 :2) (1.01 ml, 0.081 mmol of I) was added and the mixture was stirred 30 minutes. The excess of iodine was destroyed by adding 0.2 ml of aqueous sodium bisulfite 5%. The mixture was stirred 15 minutes, then it was concentrated under reduced pressure to remove all solvents. The residue was dissolved in water, washed two times with methylene chloride and once with ethyl acetate. The aqueous layer was concentrated and purified by charcoal column as follow: about 400 mg of charcoal,
20 placed over a thin layer of Celite in a funnel with fritted disk, was prewashed by passing methanol, then deionized water (by vacuum). The crude residue was diluted in a minimum of water, acidified to pH 1-2 by adding few drops of HCl 1N, then placed on the top of the charcoal column. The column was eluted with deionized water (35 ml) in order to remove inorganic salts, then 0.5 N ammonia (15 ml) to collect the desired triphosphate. The collected triphosphate was concentrated and diluted in deionized water (1 ml) and concentrated
30 NH4OH (2 ml). The mixture was stirred one hour at room temperature to cleave the acetyl group, then concentrated to dryness. The residue was purified on a pad of C18 RP silica gel eluting with deionized water (the desired triphosphate comes out fast). The fractions containing the desired triphosphate were collected and lyophilized

to give the 3'-deoxycytidine 5'-triphosphate triammonium salt as a yellowish solid (18 mg, 69% yield, purity >85% evaluated by ¹H and ³¹P-NMR). ¹H NMR (400 MHz, D₂O) δ: 7.90 (d, 1 H, 7.5 Hz), 5.99 (d, 1 H, 7.5 Hz), 5.73 (s, 1 H), 4.55 (s, 1 H), 4.35 (d, 1 H, 5.0 Hz), 4.26 (m, 1 H), 4.04 (m, 1 H), 2.05 (m, 1 H), 1.94 (m, 1 H) ppm. ³¹P NMR (162 MHz, D₂O) δ: -5.9 (br.s), -10.4 (d, 19 Hz), -21.5 (br.s) ppm. In a similar manner, the compounds of the invention can be obtained.

10

Example 2. Evaluation of Triphosphate Analogues

In The HCV RNA-Dependent RNA Polymerase Assay The following references which are referenced in the example are all incorporated by reference:

1. Behrens, S., Tomei, L., De Francesco, R. (1996) *EMBO* 15, 12-22
2. Harlow, E, and Lane, D. (1988) *Antibodies: A Laboratory Manual*. Cold Spring Harbord Laboratory. Cold Spring Harbord. NY.
- 20 3. Lohmann, V., Körner, F., Herian, U., and Bartenschlager, R. (1997) *J. Virol.* 71, 8416-8428

Compounds were evaluated using an *in vitro* polymerase assay containing purified recombinant HCV RNA-dependent RNA polymerase (NS5B protein). HCV NS5B was expressed in insect cells using a recombinant baculovirus as vector. The experimental procedures used for the cloning, expression and purification of the HCV NS5B protein are described below. Following are details of the RNA-
30 dependent RNA polymerase assays used to test the compounds.

Expression of the HCV NS5B protein in insect cells:

The cDNA encoding the entire NS5B protein of HCV-Bk strain, genotype 1b, was amplified by PCR using a plasmid

containing a cDNA version of the full-length HCV genome as template. The oligonucleotides used to amplify this HCV region were designed to introduce a *NheI* site followed by an ATG at the 5' end of the NS5B coding region as well as a *BamHI* site at the 3' end immediately downstream of the translation stop codon. The amplified sequence, of 1.8 kb, was digested with *NheI* and *BamHI* and ligated to a predigested pBlueBacII plasmid (Invitrogen). The resulting recombinant plasmid was designated

10 pBac/NS5B. Sf9 cells were co-transfected with 3 µg of pBac/NS5B, together with 1 µg of linearized baculovirus DNA (Invitrogen), as described in the manufacturer's protocol. Following two rounds of plaque purification, an NS5B-recombinant baculovirus, BacNS5B, was isolated. The presence of the recombinant NS5B protein was determined by western blot analysis (Harlow and Lane, 1988) of BacNS5B-infected Sf9 cells, using a HCV NS5B specific rabbit polyclonal antiserum (anti-NS5B). Infections of

20 Sf9 cells with this plaque purified virus were performed in one-liter spinner flasks at a cell density of 1.2×10^6 cells/ml and a multiplicity of infection of 5.

Preparation of a soluble recombinant NS5B protein:

Sf9 cells were infected as described above. Sixty hours post-infection, cells were harvested then washed twice with phosphate buffer saline (PBS). Total proteins were solubilized as described in Lohmann et al. (1989) with some modifications. In brief, proteins were extracted in

30 three steps, S1, S2, S3, using lysis buffers (LB) I, LB II and LB III (Lohmann et al, 1997). The composition of LBII was modified to contain 0.1 % triton X-100 and 150 mM NaCl to reduce the amount of solubilized NS5B protein at this step. In addition, sonication of cell extracts was avoided throughout the protocol to preserve the integrity of the protein structure.

Purification of recombinant NS5B using fast protein liquid chromatography (FPLC):

Soluble NS5B protein in the S3 fraction was diluted to lower the NaCl concentration to 300 mM, then it incubated batchwise with DEAE sepharose beads (Amersham-Pharmacia) for 2 hrs at 4°C, as described by Behrens et al. (1989). Unbound material was cleared by centrifugation for 15 min at 4°C, at 25 000 rpm using a SW41 rotor (Beckman). The
10 supernatant was further diluted to lower the NaCl concentration to 200 mM and subsequently loaded, with a flow rate of 1 ml/min, on a 5 ml HiTrap® heparin column (Amersham-Pharmacia) connected to an FPLC[±] system (Amersham-Pharmacia). Bound proteins were eluted in 1 ml fractions, using a continuous NaCl gradient of 0.2 to 1 M, over a 25 ml volume. NS5B-containing fractions were identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), followed by western blotting using the anti-NS5B antiserum at a dilution of 1:2000.
20 Positive fractions were pooled and the elution buffer was exchanged against a 50 mM NaPO₄ pH 7.0, 20 % glycerol, 0.5 % triton X-100 and 10 mM DTT, using a PD-10 column (Amersham-Pharmacia). The sample was then loaded onto a 1 ml HiTrap® SP column (Amersham-Pharmacia), with a flow rate of 0.1 ml/min. Bound proteins were eluted using a continuous 0 to 1 M NaCl gradient over a 15 ml volume. Eluted fractions were analyzed by SDS-PAGE and western blotting. Alternatively, proteins were visualized, following SDS-PAGE, by silver staining using the Silver
30 Stain Plus kit (BioRad) as described by the manufacturer. Positive fractions were tested for RdRp activity (see below) and the most active ones were pooled, and stored as a 40 % glycerol solution at -70°C.

In vitro RNA-dependent RNA polymerase assays used to evaluate the triphosphate form of nucleoside analogues:

RdRp assays were conducted using *in vitro* transcribed heteropolymeric RNA templates.

RdRp reactions were performed in a total volume of 50 μ l of a buffer consisting of 20 mM Tris-HCl pH 7.5, 1 mM DTT, 50 mM NaCl, 0.5 mM $MnCl_2$ and 5 mM $MgCl_2$. Standard HCV RdRp reactions contained 200 ng of purified NS5B protein. The substrate mixture included in the assay depended on the base of the nucleoside triphosphate to be tested (adenine, guanine, cytosine or uracil analogue).

10 The NTP substrate with a similar base to that of the inhibitor, was added at twice the measured K_m . This concentration included 5 μ Ci (3000 Ci/mmol) of a [^{32}P] version of this nucleotide. The remaining three substrates were used at 100 μ M. The measured K_m s for the four substrates were as follows: 18 μ M for ATP, 0.5 μ M for CTP and GTP, and 1.2 μ M for UTP. Following a two hour incubation at 22°C, reactions were stopped by the addition of 100 μ g of sonicated salmon sperm DNA (Life Technologies) and 1 ml of 10 % trichloroacetic acid
20 (TCA)-0.5 % tetrasodium pyrophosphate (PPi). Nucleic acids were precipitated at 4°C for 30 min after which samples were filtered on GF/C glass microfiber filters (Millipore). Membranes were subsequently washed with 25 ml of a 1% TCA-0.1 % PPi solution, then air dried. Incorporated radioactivity was quantified using a liquid scintillation counter (1450-Microbeta, Wallac).

Heteropolymeric RNA templates were generated by run-off transcription. As template for these transcription reactions, a recombinant pcDNA3 plasmid (Invitrogen)
30 containing a cDNA version of the HCV genome was used and referred to as pcDNA/HCVfl. *In vitro* transcriptions were performed using the MEGAscript™ kit (Ambion), as suggested by the manufacturer. In brief, the plasmid pcDNA/HCVfl was linearized with EcoRI to generate a truncated HCV transcript of about 6900 nucleotides. Linearized DNA was extracted with a one to one volume of

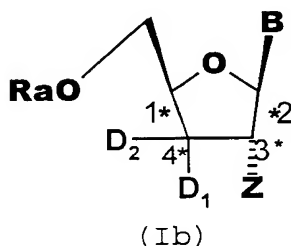
phenol/chloroform, precipitated with ethanol, then 1 µg of this linearized DNA was used as template in T7 RNA polymerase-driven in vitro transcription reactions. Transcripts were extracted using the TRIZOL® reagent (Life Technologies) and an aliquot (1 µg) was used as template in RdRp assays.

Compound	HCV polymerase
	IC ₅₀
COMPOUND#2	0.036µM
COMPOUND#4	0.3µM
COMPOUND#6	0.26µM
COMPOUND#8	1.98µM
COMPOUND#10	6.4µM
COMPOUND#12	0.048µM
COMPOUND#14	3.1µM
COMPOUND#16	0.36µM
COMPOUND#18	6.88µM
COMPOUND#20	0.18µM
COMPOUND#22	0.12µM
COMPOUND#24	0.055µM
COMPOUND#26	0.91µM
COMPOUND#28	2.1µM
COMPOUND#30	2.9µM
COMPOUND#32	6.8µM
COMPOUND#54	9.0µM

CLAIMS

We claim:

1. A method for the treatment or prevention of an hepatitis C infection in a host comprising administering a therapeutically effective amount of a compound having the formula Ib or a pharmaceutically acceptable salt thereof:

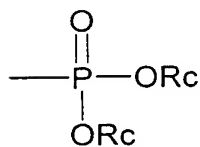


10

wherein

B is chosen from a purine, a pyrimidine or an analogue thereof;

Ra is chosen from H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, and



wherein each **Rc** are independently chosen from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl and an hydroxy protecting group; and

- 20 **Z** is **ORb**, wherein **Rb** is chosen from of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ acyl, or an hydroxy protecting group

D₁ and **D₂** are independently selected from N₃, F, or H, **D₁** and **D₂** can also be joined to be chosen from C₃-cycloalkyl, =CH₂, or =CF₂;

with the proviso that when **B** is adenine, **Z** is **ORb**, **D₁** is H, **D₂** is H and **Rb** is H, **Ra** is not triphosphate or H.

2. A method according to claim 1 wherein **Z** is OH.
3. A method according to claim 2 wherein **D₁** is H and **D₂** is F.
4. A method according to claim 2 wherein **Ra** is chosen from H, monophosphate, diphosphate, triphosphate.
- 10 5. A method according to claim 2 wherein **Ra** is triphosphate.
6. A method according to claim 2 wherein **Ra** is H.
7. A method according to claim 3 wherein **Ra** is chosen from H, monophosphate, diphosphate, triphosphate.
8. A method according to claim 3 wherein **Ra** is triphosphate.
- 20 9. A method according to claim 3 wherein **Ra** is H.
10. A method according to claim 2 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymine-1-yl, cytosine-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl, 30 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-

amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl; each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

11. A method according to claim 3 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl, 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl; each of which is unsubstituted or substituted by at least one of NHR_3 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, Br, Cl, F, I or OH, wherein R_3 is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{acyl}$.

12. A method according to claim 2 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymine-1-yl, cytosin-1-yl, 5-fluorocytosin-1-yl, uracil-1-yl, 5-fluorouracil or 1,2,4-triazole-3-carboxamide base (ribarivin base).
13. A method according to claim 3 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-
10 purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymine-1-yl, cytosin-1-yl, 5-fluorocytosin-1-yl, uracil-1-yl, 5-fluorouracil or 1,2,4-triazole-3-carboxamide base (ribarivin base).
14. A method according to claim 1 wherein the compound of formula I is chosen from:

- Compound #1:** 3'-deoxycytidine;
- Compound #2:** 3'-deoxycytidine-5'triphosphate;
- 20 **Compound #3:** 5-Fluoro-3'-deoxycytidine;
- Compound #4:** 5-Fluoro-3'-deoxycytidine-5'triphosphate;
- Compound #5:** 3'-deoxyuridine;
- Compound #6:** 3'-deoxyuridine-5'triphosphate;
- Compound #7:** 5-Fluoro-3'-deoxyuridine;
- Compound #8:** 5-Fluoro-3'-deoxyuridine-5'triphosphate;
- Compound #9:** 3'-deoxythymidine;
- Compound #10:** 3'-deoxythymidine-5'triphosphate;
- Compound #11:** 3'-deoxyguanosine;
- Compound #12:** 3'-deoxyguanosine-5'triphosphate;
- 30 **Compound #13:** 2-N-acetyl-3'-deoxyguanosine;
- Compound #14:** 2-N-acetyl-3'-deoxyguanosine-5'triphosphate;
- Compound #15:** 5-Methyl-3'-deoxycytidine;
- Compound #16:** 5-Methyl-3'-deoxycytidine-5'triphosphate;
- Compound #17:** 5-Iodo-3'-deoxycytidine;
- Compound #18:** 5-Iodo-3'-deoxycytidine-5'triphosphate;

- Compound #19: 5-Chloro-3'-deoxycytidine;
- Compound #20: 5-Chloro-3'-deoxycytidine-5'triphosphate;
- Compound #21: 3'-fluoro-3'-deoxyguanosine;
- Compound #22: 3'-fluoro-3'-deoxyguanosine -5'triphosphate;
- Compound #23: 3'-fluoro 3'-deoxycytidine;
- Compound #24: 3'-fluoro 3'-deoxycytidine-5'triphosphate;
- Compound #25: 5-Iodo-3'-deoxycytidine;
- Compound #26: 5-Iodo-3'-deoxycytidine-5'triphosphate;
- Compound #27: 5-Chloro -3'-deoxyuridine;
- 10 Compound #28: 5-Chloro -3'-deoxyuridine-5'triphosphate;
- Compound #29: 5-Bromo -3'-deoxyuridine;
- Compound #30: 5-Bromo -3'-deoxyuridine-5'triphosphate;
- Compound #31: 6-Chloro-3'-deoxyguanosine;
- Compound #32: 6-Chloro -3'-deoxyguanosine -5'triphosphate;
- Compound #33: 3'-spirocyclopropyl-3'-deoxyguanosine;
- Compound #34: 3'-spirocyclopropyl-3'-deoxyguanosine -
5'triphosphate;
- Compound #35: 3'-difluoro-spirocyclopropyl-3'-
deoxyguanosine;
- 20 Compound #36: 3'-difluoro-spirocyclopropyl-3'-
deoxyguanosine -5'triphosphate;
- Compound #37: 3'-methylene-3'-deoxyguanosine;
- Compound #38: 3'-methylene-3'-deoxyguanosine -
5'triphosphate;
- Compound #39: 3'-difluoromethylene 3'-deoxyguanosine;
- Compound #40: 3'-difluoromethylene 3'-deoxyguanosine -
5'triphosphate;
- Compound #41: 3'-spirocyclopropyl-3'-deoxycytidine;
- Compound #42: 3'-spirocyclopropyl-3'- deoxycytidine -
30 5'triphosphate;
- Compound #43: 3'-difluoro-spirocyclopropyl-3'-
deoxycytidine;
- Compound #44: 3'- difluoro-spirocyclopropyl-3'-
deoxycytidine -5'triphosphate;

- Compound #45:** 3'-methylene-3'- deoxycytidine;
Compound #46: 3'-methylene-3'- deoxycytidine -
5'triphosphate;
Compound #47: 3'-difluoromethylene 3'- deoxycytidine;
Compound #48: 3'-difluoromethylene 3'- deoxycytidine -
5'triphosphate;
Compound #49: 9-β-D-xylofuranosyl-guanosine;
Compound #50: 9-β-D-xylofuranosyl-guanosine -
5'triphosphate;
10 **Compound #51:** 9-β-D-xylofuranosyl-cytidine;
Compound #52: 9-β-D-xylofuranosyl-cytidine -
5'triphosphate;
Compound #53: 3'-azido-3'- deoxycytidine;
Compound #54: 3'-azido-3'- deoxycytidine 5'triphosphate; or
a pharmaceutically acceptable salt thereof.
15. The method according to anyone of claims 1 to 14
wherein said compound is used in combination with at
least one further therapeutic agent chosen from
20 interferon (IFN), interferon α-2a, interferon α-2b,
consensus interferon (CIFN), ribavirin, amantadine,
rimantadine, interleukine-12, ursodeoxycholic acid
(UDCA), glycyrrhizin and silybum marianum.

16. Use of a compound of formula (Ib) as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a hepatitis C infection.

17. An anti-flavivirus pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (Ib), as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

18. Use of a compound of formula (Ib) as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a Flavivirus infection.

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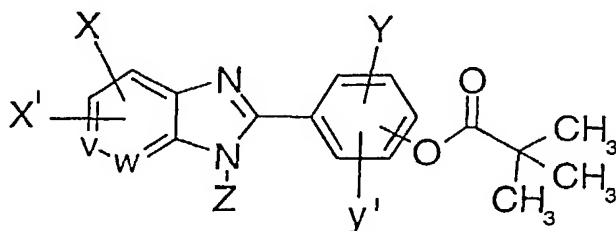
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(54) Title: ESTER DERIVATIVES OF DIMETHYLPROPIONIC ACID AND PHARMACETUICAL COMPOSITIONS CON-
TAINING THEM



(I)

(57) Abstract: The present invention relates to esters of 2,2-dimethylpropionic acid having the general formula (I) or pharmacological acceptable salts thereof, as well as to pharmaceutical compositions containing said compounds and having an inhibitory activity of elastase.

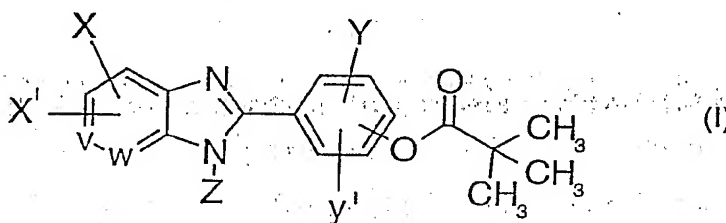


WO 01/66526 A1

Ester derivatives of dimethylpropionic acid and pharmaceutical compositions containing them ---

The present invention relates to new esters of 2,2-dimethylpropionic acids, to the use thereof as agents having an inhibitory activity of elastase and to pharmaceutical compositions containing these compounds or a pharmaceutically acceptable salt thereof.

More particularly, the object of the invention consists in compounds of general formula (I),



or a pharmaceutically acceptable salt thereof, where

x and x' represent a hydrogen atom, an alkyl group in C1-C4, an halogen atom or a group nitro;

y and y' represent a hydrogen atom, a group alkyl in C1-C4, a group alkoxy in C1-C4, an halogen atom or a group dialkyl(C1-C4)amino;

z represents a hydrogen atom, a dialkyl(C1-C4)aminoalkyl(C1-C4) group or a piperidiny-alkyl(C1-C4) group; and

v and w represent a carbon atom bound to a hydrogen atom (CH) or a nitrogen atom substituted or not.

More particularly, in the above formula (I), the definition of the substituents may be the following :

x and/or x' represent the group methyl or nitro, or a chlorine atom;

y and/or y' represent the group methyl, methoxy, nitro or diethylamino, or a chlorine, a bromine or a fluorine atom; and

z represents a group dimethylaminoethyl, dimethylaminopropyl, diisopropylaminoethyl or piperidinyl-ethyl.

In these compounds of formula (I), v or w may represent a nitrogen atom substituted by a group methyl, ethyl, benzyl, piperidinyl-ethyl, piperidinyl-propyl, bis(fluorophenyl)methyl-piperazinyl-ethyl or bis(fluorophenyl)methyl-piperazinyl-propyl.

Some specific examples of the compounds of the present invention, without setting a limit to it, are the followings:

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-ethoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2,6-dimethoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-chloro-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-nitro-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-nitro-6-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5-chloro-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-methyl-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-methyl-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5,6-dimethyl-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5-nitro-1H-benzimidazol-2-yl)phenyl ester

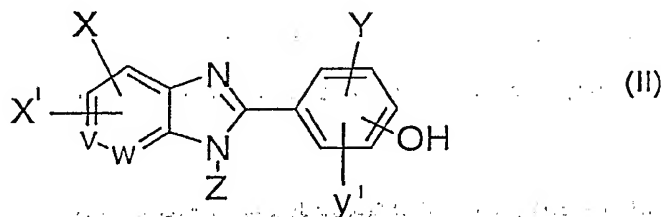
2,2-Dimethyl-propionic acid 4-(5-nitro-1H-benzimidazol-2-yl)-6-methoxy-2-nitro-phenyl ester

- 2,2-Dimethylpropionic acid 4-[1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl] phenyl ester.
- 2,2-Dimethylpropionic acid 2-bromo-4-[1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester
- 2,2-Dimethylpropionic acid 4-[1-(2-dimethylaminopropyl)-1H-benzimidazol-2-yl]phenyl ester, dihydrogen oxalate
- 2,2-Dimethylpropionic acid 4-[1-(2-diisopropylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester.
- 2,2-Dimethylpropionic acid 4-[5,6-dichloro-1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl] phenyl ester
- 2,2-Dimethylpropionic acid 4-[5,6-dimethyl-3-(2-piperidin-1-yl-ethyl)-1H-benzimidazol-2-yl] phenyl ester
- 2,2-Dimethylpropionic acid 2-fluoro-4-[1-(2-piperidin-1-yl ethyl)-1H-benzimidazol-2-yl] phenyl ester
- 2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)phenyl ester
- 2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-4-chloro-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-5-chloro-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-4,6-dichloro-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-6-methoxy-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5-chloro-1H-benzimidazol-2-yl)phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5-chloro-1H-benzimidazol-2-yl)-5-diethylamino-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5-methyl-1H-benzimidazol-2-yl)-4-chloro-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5,6-dimethyl-1H-benzimidazol-2-yl)-diethylamino-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-4-chloro-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-6-methyl-phenyl ester
- 2,2-Dimethyl-propionic acid 5-(1H-benzimidazol-2-yl)-phenyl ester
- 2,2-Dimethyl-propionic acid 3-(1H-benzimidazol-2-yl)-6-methoxy-phenyl ester

- 2,2-Dimethyl-propionic acid 3-(1H-benzimidazol-2-yl)-4-nitro-phenyl ester
- 2,2-Dimethyl-propionic acid 3-(5-chloro-1H-benzimidazol-2-yl)phenyl ester
- 2,2-Dimethyl-propionic acid 3-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester
- 2,2-Dimethyl-propionic acid 3-(5-nitro-1H-benzimidazol-2-yl)phenyl ester
- 2,2-Dimethyl-propionic acid 3-(5-nitro-1H-benzimidazol-2-yl)-4-nitro-phenyl ester
- 2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester
- 2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-b]pyridin-2-yl)-2-methoxy-phenyl ester
- 2,2-Dimethyl-propionic acid 2-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester
- 2,2-Dimethyl-propionic acid 3-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester
- 2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester
- 2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-c]pyridin-2-yl)-2-methoxy-phenyl ester
- 2,2-Dimethyl-propionic acid 3-(3H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester
- 2,2-Dimethylpropionic acid 4-(5-methyl-5H-imidazo[4,5-c]pyridin-2-yl) phenyl ester.
- 2,2-Dimethylpropionic acid 4-(5-ethyl-5H-imidazo[4,5-c]pyridin-2-yl) phenyl ester, hydrogen oxalate
- 2,2-Dimethylpropionic acid 4-(5-benzyl-5H-imidazo[4,5-c]pyridin-2-yl)phenyl ester
- 2,2-Dimethylpropionic acid 4-[5-(2-piperidin-1-yl ethyl)-5H-imidazo[4,5-c]pyridin-2-yl] phenyl ester
- 2,2-Dimethylpropionic acid 4-[5-(2-piperidin-1-yl propyl)-5H-imidazo[4,5-c] pyridin-2-yl] phenyl ester
- 2,2-dimethylpropionic acid 4-[5-(3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-ethyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl-ester
- 2,2-Dimethyl-propionic acid 4-[5-(3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-propyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl ester
- 2,2-Dimethyl-propionic acid 4-[(1-H-benzimidazol-2-yl)-2,2-dimethyl-propionyloxy]-phenyl ester

The new compounds can be obtained with usual known methods, which are already described in the literature, for the esterification of phenolic derivatives, with

2,2-dimethylpropionic acid or its corresponding acid chloride or anhydride. In that way, a compound with general formula (II)



where x, x', y, y', z, v and w are as defined above, is reacted with 2,2-dimethylpropionic acid or its acid chloride or its anhydride to afford a compound with general formula (I).

The methods used for esterification of the general formula (II) compounds, with 2,2-dimethylpropionic acid derivatives can be those described for example in EP patents 0 649 846 or 0 347 168.

More generally, the following methods used to obtain the intermediate compounds with general formula (II) can be mentioned :

- Haugwitz, R.D.; Maurer, B.V.; Jacobs, G.A.; Marayanan, V.L.;

J. Med. Chem., (1979), Vol. 22, No. 9, 1113.

- Yildir, I.; Uzbay, T.; Noyanalpan, N.; *J. Fac. Pharm. Gazi*, vol. 7, No. 2, 111-24 (1990). – Perginer, H.; Abbasoglu, U.; Noyanalpan, N.; *J. Fac. Pharm.*

Gazi, vol. 7, No. 2, 125-40 (1990).

- Kumazawa, T.; Harakawa, H.; Fukui, H. et al.; *Bioorg. Med. Chem. Lett.* Vol. 5, No. 16, 1829-32 (1995).

- Ohalopathy, C.V.; Veeranagaiah, V.; Kondal, K.; Subba Rao, N.V., *Indian J. of Chem.*, vol. 17B, June 1979, 566-8. – Ueda, M.; Sato, M.; Mochizuki, A.; *Macromolecules*, (1985), vol. 18, 2723-6.

- Sluka, J.; Novak, J.; Budesinsky, Z.; *Coll. Czech. Chem. Commun.*, vol. 41, 3628-34 (1976).

The pharmacologically acceptable salts produced by addition of acids to the compounds with general formula (I) are prepared in the conventional way, that is through addition to a free base (I) solution or suspension, of one or two equivalents of a pharmacologically acceptable organic or inorganic acid.

Examples of acids are : hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, lactic, *p*-toluensulphonic, gluconic, fumaric, succinic, ascorbic, maleic, methanesulphonic and benzenesulphonic. The salts afforded by addition of acids can be advantageous, due to some of their physical properties just as high solubility in polar solvents like, for example, water. This would facilitate preparations which include the product administration dissolved in water.

The compounds (I) of the present patent can be used as pharmaceutical agents having an inhibitory activity of elastase, and therefore be administered either solely, or more generally mixed with a pharmacological coadjuvant, chosen in agreement with the administration way and the standard pharmacological practice. For example, they can be administered by oral via in form of either tablets which contain excipients, just as starch or lactose, or capsules, solely or mixed with excipients, or sirups or suspensions which contain colorant or aromatic agents. Also, they can be injected by parenteral via, for example, intramuscular, intravenous or subcutaneously. In the parenteral administration, they can be used preferably in the form of sterile aqueous solution, which can contain another solutes, for example, glucose or any salt, in order to make the solution isotonic.

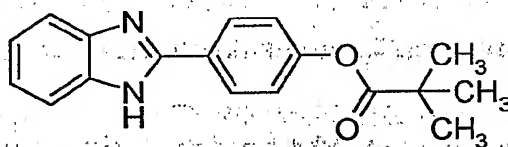
The pharmacological compositions will be able to contain a quantity of some of the compounds with general formula (I), so that the dose level administrated is comprised between 0,001 and 10 mg/kg. The active principle quantity in each dose form will be comprised approximately between 0.05 and 1 mg or between

0.1 and 99% by weight of the preparation, preferably between 2 and 50% by weight for oral preparations. The active substance dose per day depends on the administration form. In general, between 50 and 100mg/day are administered by oral via. While the intramuscular administration can be provided in a single dose or divided in up to 3 doses, the intravenous administration can include a dropper for its dosification in continuous. Necessarily, there will be variations which would depend on the weight and subject conditions to be treated and the particular administration via.

The following examples illustrate the present invention without setting limits to it:

Example 1

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-phenyl ester

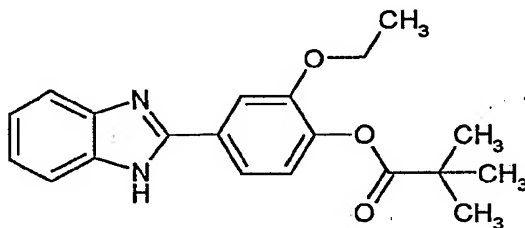


Initially, 35 mL of triethylamine were added dropwise to a stirred solution of 20 g (0.095 mol) of 2-(4-hydroxyphenyl)benzimidazole in 115 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath. Then, 11.47 g (0.095 mol) of 2, 2-dimethylpropionyl chloride were dropwise added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 4 additional hours. Finally, 100 mL of ethyl eter were added to the reaction mixture, the insoluble residue was filtered off, and the remaining liquid was washed with H_2O (2 x 250 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 . Then, after evaporating the solvent under reduced pressure, the product was isolated as a white solid with m.p. $308-10^\circ\text{C}$ (recrystallized in ethanol) with a yield of 85 %.

<u>Quantitative Analysis:</u>		Calculated for $C_{18}H_{18}N_2O_2$		
		% C	% H	% N
Calculated:		73.45	6.16	9.52
Found:		73.34	6.37	9.31

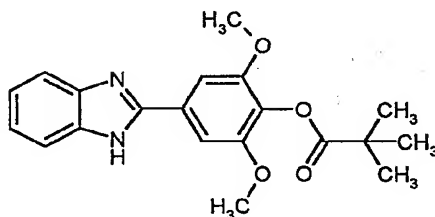
Example 2

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-ethoxy-phenyl ester



Initially, 14 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.039 mol) of 2-(3-ethoxy-4-hydroxyphenyl)benzimidazole in 47 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.74 g (0.039 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about $0^\circ C$ for 30 minutes and then, at room temperature for 7 hours. At the end, 75 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was isolated as a solid with m.p. $180-1^\circ C$ (recrystallized in ethanol) with a yield of 52%.

<u>Quantitative Analysis:</u>		Calculated for $C_{20}H_{22}N_2O_3$		
		% C	% H	% N
Calculated:		70.99	6.55	8.28
Found:		70.69	6.61	8.07

Example 3**2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2,6-dimethoxy-phenyl ester**

Initially, 7 mL of triethylamine were added dropwise to a stirred solution composed of 5 g (0.018 mol) of 2-(3,5-dimethoxy-4-hydroxyphenyl)benzimidazole in 23 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 2.23 g (0.018 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 6 hours. Finally, 40 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product was obtained as a solid with m.p. $243-5^\circ\text{C}$ (recrystallized in methanol) with a yield of 45%.

Quantitative Analysis:Calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4$

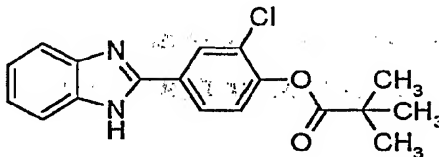
Calculated:

% C % H % N

67.78 6.26 7.90

Found:

67.48 6.39 7.72

Example 4**2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-chloro-phenyl ester**

Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution composed of 8.76 g (0.036 mol) of 2-(3-chloro-4-hydroxyphenyl)benzimidazole in

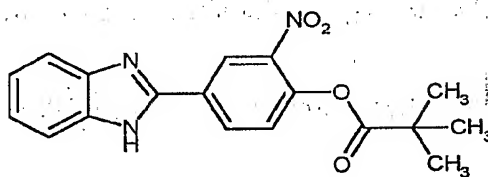
45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.32 g (0.036 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes, and then, at room temperature for 4 hours. After that, 75 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was obtained as a solid with m.p. $206-8^\circ\text{C}$ (recrystallized in methanol) with a yield of 74%, with 1/2 methanol molecule.

Quantitative Analysis. Calculated for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2 \cdot 1/2\text{CH}_4\text{O}$

	% C	% H	% N
Calculated:	64.44	5.55	8.12
Found:	64.35	6.20	7.97

Example 5

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-nitro-phenyl ester



Initially, 12 mL of triethylamine were added dropwise to a stirred solution composed of 8 g (0.031 mol) of 2-(3-nitro-4-hydroxyphenyl)benzimidazole in 40 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath. Then, 3.78 g (0.031 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes, and next, at room temperature for 4 hours. After that, 70 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product was obtained as a solid with m.p. $185-7^\circ\text{C}$ (recrystallized in methanol) with a yield of 65%.

Quantitative Analysis:

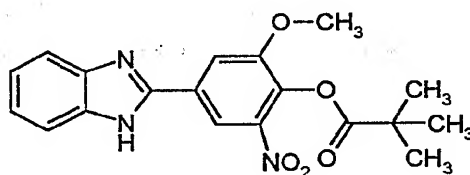
Calculated:
Found:

Calculated for $C_{18}H_{17}N_3O_4$

% C	% H	% N
63.71	5.05	12.38
63.69	5.28	12.24

Example 6

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-nitro-6-methoxy-phenyl ester



Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.035 mol) of 2-(4-hydroxy-5-methoxy-3-nitrophenyl)benzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.23 g (0.035 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the mixture was stirred at about $0^\circ C$ for 30 minutes and next, at room temperature for 8 hours. Finally, 45 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the remaining liquid was washed with H_2O (2 x 200 mL). The organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product was obtained as a solid with m.p. $190-2^\circ C$ (recrystallized in ethyl acetate) with a yield of 50%.

Quantitative Analysis:

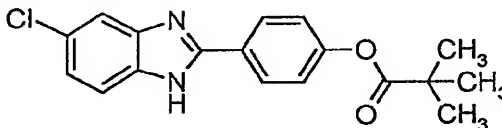
Calculated:
Found:

Calculated for $C_{19}H_{19}N_3O_5$

% C	% H	% N
61.78	5.18	11.38
62.02	5.51	11.04

Example 7

2,2-Dimethyl-propionic acid 4-(5-Chloro-1H-benzimidazol-2-yl)phenyl ester



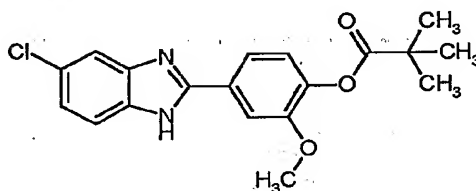
Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution of 8.76 g (0.036 mol) of 2-(4-hydroxyphenyl)-5-chlorobenzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.32 g (0.036 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 8 hours. After such a time, 75 mL of ethyl eter were added to the mixture, the insoluble residue was filtered off, and the remaining liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. $247-9^\circ\text{C}$ (recrystallized in ethanol) with a yield of 69%.

Quantitative Analysis

	Calculated for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$		
	% C	% H	% N
Calculated:	65.75	5.21	8.52
Found:	66.04	5.04	8.43

Example 8

2,2-Dimethyl-propionic acid 4-(5-Chloro-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester



Initially, 15 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.036 mol) of 2-(4-hydroxy-3-methoxyphenyl)-5-chlorobenzimidazole in 50

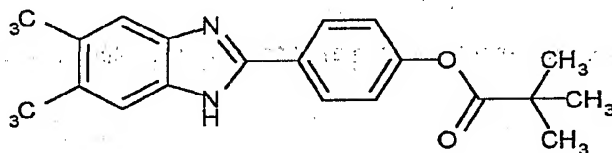
mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 2.43 g (0.020 mol) of trimethylacetyl chloride. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 4 hours. After such a time, 50 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered and the liquid was washed with H_2O (2 x 125 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was obtained as a solid with m.p. = $197-9^\circ\text{C}$ (recrystallized in methanol) with a yield of 71%.

Quantitative Analysis: Calculated for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_3$

	% C	% H	% N
Calculated:	63.60	5.34	7.81
Found:	63.58	5.43	7.80

Example 9

2,2-Dimethyl-propionic acid 4-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester



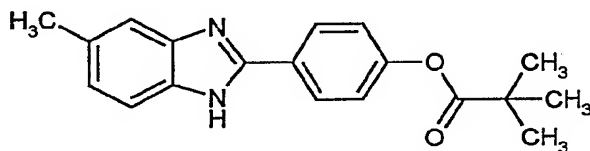
Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution composed of 8.54 g (0.036 mol) of 2-(4-hydroxyphenyl)-5,6-dimethylbenzimidazole in 45 mL of anhydrous CH_2Cl_2 using external cooling with an ice-water bath, and next, 4.32 g (0.036 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 8 hours. After that, 75 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure and the product was obtained as a solid with m.p. $231-3^\circ\text{C}$ (recrystallized in ethanol/water) with a yield of 59%.

Quantitative Analysis:

	Calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$		
	% C	% H	% N
Calculated:	74.51	6.88	8.69
Found:	74.26	7.35	8.62

Example 10

2,2-Dimethyl-propionic acid 4-(5-methyl-1H-benzimidazol-2-yl)phenyl ester



Initially, 16 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.045 mol) of 2-(4-hydroxyphenyl)-5-methylbenzimidazole in 55 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 5.38 g (0.045 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and, then, at room temperature for 14 hours. Finally, 100 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 125 mL). The organic phase were dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure and the product was isolated as a solid with m.p. $235-7^\circ\text{C}$ (recrystallized in ethyl acetate with a yield of 55 %),

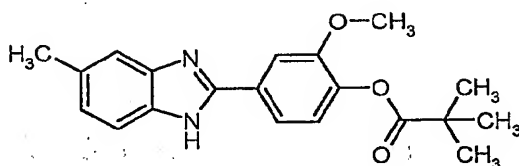
Quantitative Analysis :

Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$

	% C	% H	% N
Calculated:	74.00	6.54	9.08
Found:	74.32	6.61	9.19

Example 11

2,2-Dimethyl-propionic acid 4-(5-methyl-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester



Initially, 15 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.039 mol) of 2-(4-hydroxy-3-methoxyphenyl)-5-methylbenzimidazole in 50 mL of anhydrous CH_2Cl_2 , using external cooling with an ice water bath. Then, 4.74

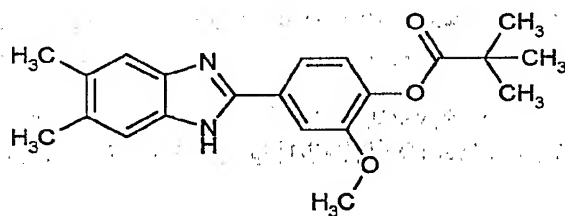
g. (0.024 mol) of trimethylacetyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and, next, at room temperature for 4 hours. At the end, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H₂O (2 x 100 mL). The organic phase was dried over Na₂SO₄, the solvent evaporated under reduced pressure and the product obtained as a solid with m.p. 186-8°C (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 59%.

Quantitative Analysis:

	Calculated for C ₂₀ H ₂₂ N ₂ O ₃		
	% C	% H	% N
Calculated:	70.99	6.55	8.28
Found:	70.98	6.61	8.02

Example 12

2,2-Dimethyl-propionic acid 4-(5,6-dimethyl-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester



Initially, 14 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.037 mol) of 2-(4-hydroxy-3-methoxyphenyl)-5,6-dimethylbenzimidazole in 50 mL of anhydrous CH₂Cl₂, using external cooling with an ice-water bath, and then, 4.49 g (0.037 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes, and then, at room temperature for 4 hours. After such a time, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H₂O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na₂SO₄, the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. = 177-9°C (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 70%.

Quantitative Analysis:Calculated for $C_{21}H_{24}N_2O_3$

Calculated:

% C % H % N

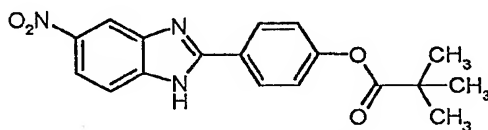
71.57 6.86 7.95

Found:

71.03 7.10 7.69

Example 13

2,2-Dimethyl-propionic acid 4-(5-nitro-1H-benzimidazol-2-yl)phenyl ester



Initially, 0,5 g (0.004 mol) of 4-dimethylaminopyridine were added dropwise to a stirred solution of 10.21 g (0.04 mol) of 2-(4-hydroxy)-5-nitrobenzimidazole in 60 mL of anhydrous $CHCl_3$, using external cooling with an ice-water bath, and next, 7.45 g (0.04 mol) of 2, 2-dimethylpropionyl anhydride. Once the addition was completed, the mixture was stirred at room temperature for 12 hours. After such a time, about 40 ml of the solvent were evaporated under reduced pressure, and the resultant mixture was cooled at $-10^\circ C$ overnight. Then, the crystallized product was separated by filtration, yielding a solid with m.p. $198-200^\circ C$ (recrystallized in ethyl acetate) with a yield of 33%.

Quantitative Analysis:Calculated for $C_{18}H_{17}N_3O_4$

Calculated:

% C % H % N

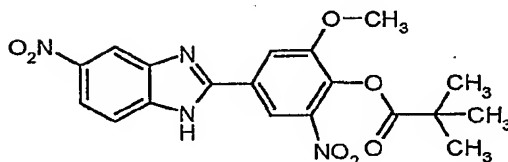
63.71 5.05 12.38

Found:

63.19 5.23 12.20

Example 14

2,2-Dimethyl-propionic acid 4-(5-nitro-1H-benzimidazol-2-yl)-6-methoxy-2-nitro-phenyl ester



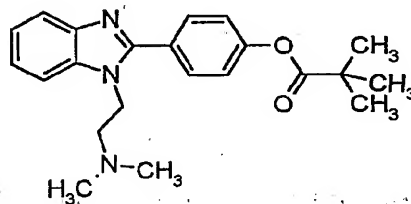
Initially, 11 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.03 mol) of 2-(4-hydroxy-5-methoxy-3-nitrophenyl)-5-nitrobenzimidazole in 38 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 3.65 g (0.03 mol) of 2,2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 8 hours. Then, 40 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 175 mL). Finally, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. $243-5^\circ\text{C}$ (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 49%.

Quantitative Analysis:Calculated for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_7$

	% C	% H	% N
Calculated:	55.07	4.38	13.52
Found:	55.08	4.39	13.24

Example 15

2,2-Dimethylpropionic acid 4-[1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester. (MAH-1)



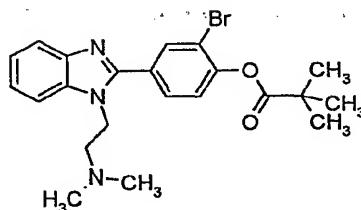
To a stirred solution of the 4-[1-(2-dimethylamino-ethyl)-1H-benzimidazol-2-yl]phenol (0.5 g, 1.78 mmol) and NaOH (0.36 g, 8.89 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added pivaloyl chloride (0.32 g, 2.67 mmol). The mixture was stirred for 5 h and then H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/acetone (5/1) to give a white solid, which was recrystallized from diethyl ether, and had a melting point of 107-109 °C. Yield: 86%

Quantitative Analysis: Calculated for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2$ (365.48 g/mol)

	% C	% H	% N
Calculated:	72.30	7.45	11.50
Found:	72.49	7.50	11.20

Example 16

2,2-Dimethylpropionic acid 2-Bromo-4-[1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester. (MAH-4)



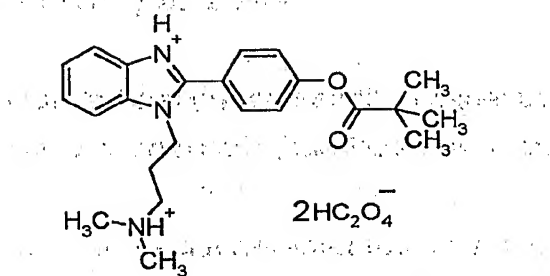
To a stirred solution of the 2-bromo-4-[1-(2-dimethylamino-ethyl)-1H-benzimidazol-2-yl]phenol (0.65 g, 1.78 mmol) and NaOH (0.36 g, 8.89 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added pivaloyl chloride (0.32 g, 2.67 mmol). The mixture was stirred for 5 h and then H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using as eluent EtOAc/acetone (5/1) to give a white solid, which was recrystallized from hexane, giving a melting point of 117-118 °C. Yield: 75%.

Quantitative Analysis : Calculated for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2$ (379.50 g/mol):

	%C	%H	%N
Calculated:	59.46	5.90	9.46
Found:	59.08	5.78	9.86

Example 17

2,2-Dimethylpropionic acid 4-[1-(2-dimethylaminopropyl)-1H-benzimidazol-2-yl]phenyl ester, dihydrogen oxalate. (MAH-2)



To a stirred solution of the 4-[1-(2-dimethylamino-propyl)-1H-benzimidazol-2-yl]phenol (0.52 g, 1.78 mmol) and NaOH (0.36 g, 8.89 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added pivaloyl chloride (0.32 g, 2.67 mmol). The mixture was stirred for 5 h and then H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel,

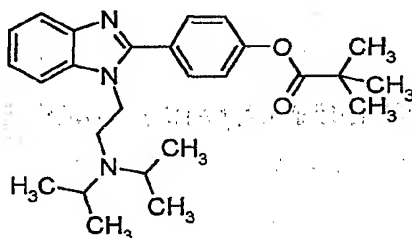
eluting with acetone to give a colourless oil, which was isolated as oxalate. The salt was recrystallized from EtOH, giving a melting point of 157-159 °C. Yield: 54%

Quantitative Analysis : Calculated for $C_{27}H_{33}N_3O_{10} \cdot H_2O$ (577.59 g/mol) :

	%C	%H	%N
Calculated:	56.14	6.11	7.27
Found:	56.50	6.02	7.25

Example 18

2,2-Dimethylpropionic acid 4-[1-(2-diisopropylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester. (MAH-3)



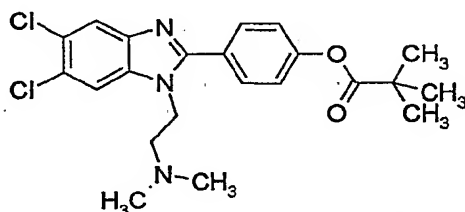
To a stirred solution of the 4-[1-(2-diisopropylamino-ethyl)-1H-benzimidazol-2-yl]phenol (0.6 g, 1.78 mmol) and NaOH (0.36 g, 8.89 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added pivaloyl chloride (0.32 g, 2.67 mmol). The mixture was stirred for 5 h and then H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using as eluent hexane/EtOAc (7/3) to give a white solid, which was recrystallized from hexane, giving a melting point of 143-144 °C. Yield: 70%.

Quantitative Analysis : Calculated for $C_{26}H_{35}N_3O_2$ (421.58 g/mol)

	%C	%H	%N
Calculated:	74.07	8.37	9.97
Found:	73.67	8.28	10.31

Example 19

2,2-Dimethylpropionic acid 4-[5,6-dichloro-1-(2-dimethylaminoethyl) 1H-benzimidazol-2-yl] phenyl ester. (MAH-7)



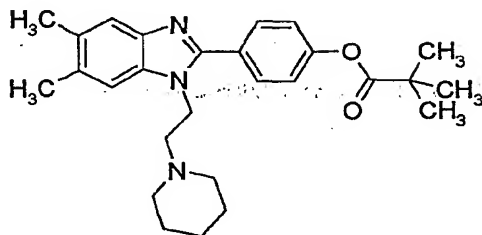
To a stirred solution of the 4-[5,6-dichloro-3-(2-dimethylamino-ethyl)-1H-benzimidazol-2-yl]phenol (1g, 2.8 mmol) and NaOH (0.57 g , 14.2 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added pivaloyl chloride (0.67 g, 5.67 mmol). The mixture was stirred for 5 h and then H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel , eluting with EtOAc to give a white solid, which was recrystallized from hexane, giving a melting point of 140-141 °C. Yield: 59%.

Quantitative Analysis : Calculated for $\text{C}_{22}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_2$ (434.37 g/mol)

	%C	%H	%N
Calculated:	60.83	5.80	9.67
Found:	60.55	6.14	9.63

Example 20

2,2-Dimethylpropionic acid 4-[5,6-dimethyl-3-(2-piperidin-1-yl-ethyl)-1H-benzimidazol-2-yl] phenyl ester. (MAH-8)



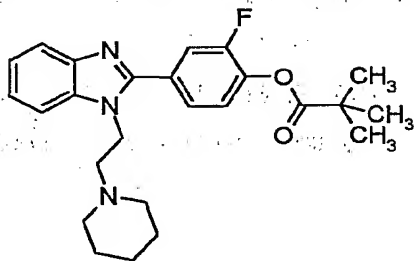
To a stirred solution of the 4-[5,6-dimethyl-3-(2-dimethylamino-ethyl)-1H-benzimidazol-2-yl]phenol (1.2 g, 3.4 mmol) and NaOH (1.17 g , 17.2 mmol) in dry CH_2Cl_2 (100 mL) at room temperature was added pivaloyl chloride (0.82 g, 6.86 mmol). The mixture was stirred for 5 h and then H_2O (150 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel , eluting with EtOAc to give a white solid, which was recrystallized from hexane, giving a melting point of 144-145 °C. Yield: 74%.

Quantitative Analysis : Calculated for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_2$ (433.59 g/mol) :

	%C	%H	%N
Calculated:	74.79	8.14	9.69
Found:	74.86	8.43	9.48

Example 21

2,2-Dimethylpropionic acid 2-fluoro-4-[1-(2-piperidin-1-yl ethyl)-1H-benzimidazol-2-yl] phenyl ester. (MAH-10)



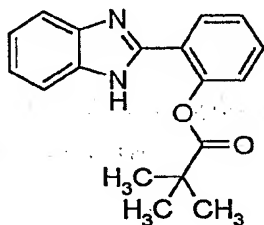
To a stirred solution of the 4-[3-(2-dimethylamino-ethyl)-1H-benzimidazol-2-yl]-2-fluorophenol (1.4 g, 4.15 mmol) and NaOH (0.82 g , 20.7 mmol) in dry CH_2Cl_2 (100 mL) at room temperature was added pivaloyl chloride (1.0 g, 8.29 mmol). The mixture was stirred for 5 h and then H_2O (150 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc to give a white solid, which was recrystallized from hexane, giving a melting point of 147-148 °C. Yield: 68%.

Quantitative Analysis : Calculated for $C_{25}H_{30}FN_3O_2$ (423.53 g/mol) :

	%C	%H	%N
Calculated:	70.90	7.14	9.92
Found:	70.76	7.18	9.98

Example 22

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)phenyl ester



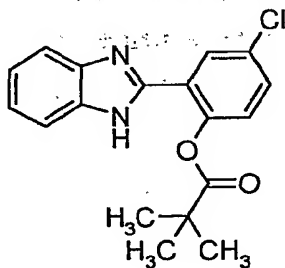
Initially, 18 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.048 mol) of 2-(2-hydroxyphenyl)benzimidazole in 60 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath. Then, 5.73 g (0.048 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about $0^\circ C$ for 30 minutes and then, at room temperature for 8 hours. At the end, 100 mL of ethyl ether were added to the reaction mixture; the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 150 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 . Finally, after evaporating the solvent under reduced pressure, the product was isolated as a solid with m.p. $147-9^\circ C$ (recrystallized in ethyl acetate) with a yield of 73%.

Quantitative Analysis: Calculated for $C_{18}H_{18}N_2O_2$

	% C	% H	% N
Calculated:	73.45	6.16	9.52
Found:	73.72	6.30	9.44

Example 23

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-4-chloro-phenyl ester



Initially, 376.2 g (4.76 mol) of pyridine were added dropwise to a stirred solution of 116.4 g (0.48 mol) of 2-(3-chloro-6-hydroxyphenyl)benzimidazole in 750 mL of anhydrous acetone, using external cooling with an ice-water bath, and then, 573.5 g (4.76 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the resultant mixture was stirred at room temperature for 6 hours. At the end, the reaction mixture was poured into water-ice (1.5 L), and the resulting solution was made alkaline with K_2CO_3 . Finally, the precipitate was filtered and washed with H_2O , until liquids appear neutral. In this way, the product was obtained as a solid with m.p. 189-91°C (recrystallized in ethyl acetate) with a yield of 71%

Quantitative Analysis:Calculated for $C_{18}H_{17}ClN_2O_2$

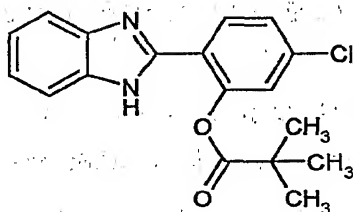
% C % H % N

Calculated: 65.75 5.21 8.52

Found: 65.71 5.28 8.31

Example 24

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-5-chloro-phenyl ester



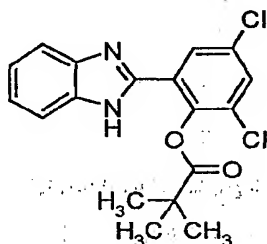
Initially, 14 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.041 mol) of 2-(4-chloro-2-hydroxyphenyl)benzimidazole in 47 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.93 g (0.041 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resulting mixture was stirred at about 0°C for 30 minutes and, then, at room temperature for 4 hours. After such a time, 45 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over Na_2SO_4 , the solvent evaporated under reduced pressure and the product was obtained as a solid with m.p. 147-9°C (recrystallized in diisopropyl ether) with a yield of 56 %.

Quantitative Analysis :

	Calculated for $C_{18}H_{17}ClN_2O_2$		
	% C	% H	% N
Calculated:	65.75	5.21	8.52
Found:	65.84	5.29	8.51

Example 25

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-4,6-dichloro-phenyl ester



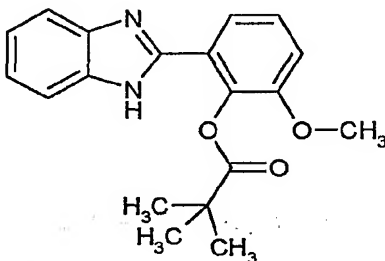
Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.036 mol) of 2-(3,5-dichloro-2-hydroxyphenyl)benzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath. Then, 4.32 g (0.036 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at $0^\circ C$ for 30 minutes and then, at room temperature for 11 hours more. After that, 75 mL of ethyl ether were added to the reaction mixture; the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 . Finally, after evaporating the solvent under reduced pressure, the product was isolated as a solid with m.p. $220-2^\circ C$ (recrystallized in ethanol) with a yield of 67 %.

Quantitative Analysis:

	Calculated for $C_{18}H_{16}Cl_2N_2O_2$		
	% C	% H	% N
Calculated:	59.52	4.44	7.71
Found:	59.86	4.67	7.98

Example 26

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-6-methoxy-phenyl ester



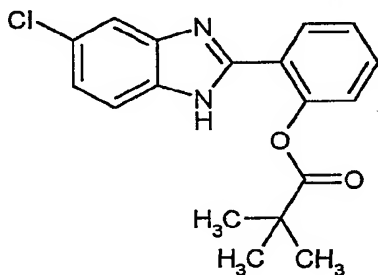
Initially, 15 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.042 mol) of 2-(2-hydroxy-3-methoxyphenyl)benzimidazole in 51 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 5.02 g (0.042 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 4 hours. Then, 45 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. $158-60^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 82%.

Quantitative Analysis:

	Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$		
	% C	% H	% N
Calculated:	70.35	6.21	8.64
Found:	70.74	6.28	8.62

Example 27

2,2-Dimethyl-propionic acid 2-(5-chloro-1H-benzimidazol-2-yl)phenyl ester



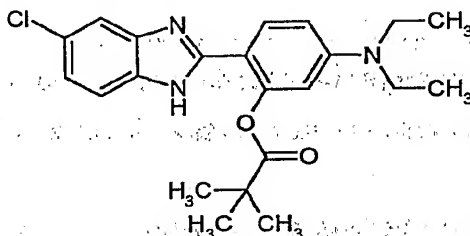
Initially, 12 mL of triethylamine were added dropwise to a stirred solution composed of 8 g (0.033 mol) of 2-(2-hydroxyphenyl)-5-chlorobenzimidazole in 40 mL of anhydrous CH_2Cl_2 using external cooling with an ice-water bath, and next, 3.94 g (0.033 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the resultant mixture was stirred at about 0 °C for 30 minutes and then, at room temperature for 8 hours. Finally, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product was obtained as a solid with m.p. 178-80 °C (recrystallized in ethyl acetate) with a yield of 49%.

Quantitative Analysis: Calculated for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$

	% C	% H	% N
Calculated:	65.75	5.21	8.52
Found:	65.52	5.42	8.46

Example 28

2,2-Dimethyl-propionic acid 2-(-5-chloro-1H-benzimidazol-2-yl)-5-diethylamino-phenyl ester



Initially, 6 mL of triethylamine were added dropwise to a stirred solution composed of 4.5 g (0.014 mol) of 2-(2-hydroxy-4-diethylamino)-5-chlorobenzimidazole in 30 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 1.89 g (0.016 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture were stirred at about 0°C for 30 minutes and then, at room temperature for 4 hours. Then, 20 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the filtered liquid was washed with H_2O (2 x 50 mL). The organic phase

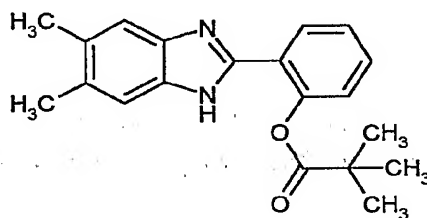
was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product was obtained as a solid with m.p. $194-6^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 66%.

Quantitative Analysis:Calculated for $\text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_2$

	% C	% H	% N
Calculated:	66.07	6.55	10.51
Found:	66.12	6.67	10.39

Example 29

2,2-Dimethyl-propionic acid 2-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester.



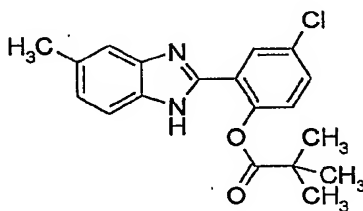
Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution of 8.71 g (0.037 mol) of 2-(2-hydroxyphenyl)-5,6-dimethylbenzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.4 g (0.037 mol) of 2,2-dimethylpropionyl chloride were added. Once the addition was completed, the resulting mixture was stirred for about 0°C for 30 minutes, and then, at room temperature for 5 hours. After that, 75 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 200 mL). The organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. $132-4^\circ\text{C}$ (recrystallized in diisopropyl ether) with a yield of 65 %.

Quantitative Analysis :Calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$

	%C	%H	%N
Calculated:	74.51	6.88	8.69
Found:	74.81	7.24	8.69

Example 30

2,2-Dimethyl-propionic acid 2-(5-methyl-1H-benzimidazol-2-yl)-4-chloro-phenyl ester



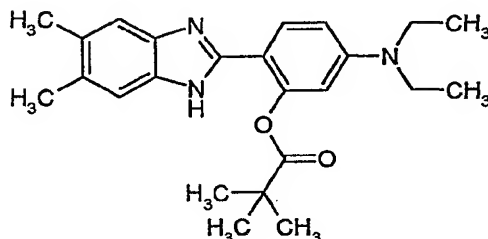
Initially, 15 mL of triethylamine were added dropwise to a stirred solution of 7 g (0.027 mol) of 2-(3-chloro-6-hydroxyphenyl)-5-methylbenzimidazole in 50 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.49 g (0.037 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 4 hours. After such a time, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered and the remaining liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was obtained as a solid with m.p. $162-4^\circ\text{C}$ (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 59%.

Quantitative Analysis: Calculated for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_2$

	% C	% H	% N
Calculated:	66.57	5.59	8.17
Found:	66.52	5.67	8.13

Example 31

2,2-Dimethyl-propionic acid 2-(5,6-dimethyl-1H-benzimidazol-2-yl)-diethylamino-phenyl ester



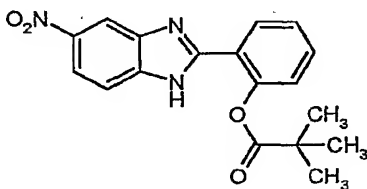
Initially, 7.5 mL of triethylamine were added dropwise to a stirred solution of 4.15 g (0.013 mol) of 2-(2-hydroxy-4-diethylaminophenyl)-5,6-dimethylbenzimidazole in 25 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 2.43 g (0.020 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 4 hours. After such a time, 25 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 50 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was obtained as a solid with m.p. = $160-2^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 61%.

Quantitative Analysis:

	Calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_2$		
	% C	% H	% N
Calculated:	73.25	7.94	10.68
Found:	73.24	7.63	11.21

Example 32

2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-phenyl ester



Initially, 14 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.039 mol) of 2-(2-hydroxyphenyl)-5-nitrobenzimidazole in 50 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 7.09 g (0.059 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes, and then, at room temperature for 4 hours. After such a time, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. = $156-8^\circ\text{C}$ (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 49%.

Quantitative Analysis:

Calculated:

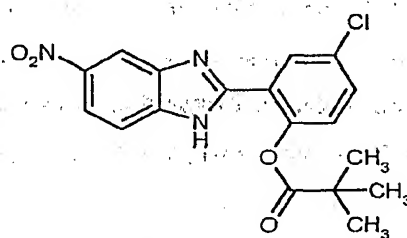
Found:

Calculated for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$

% C	% H	% N
63.71	5.05	12.38
63.81	5.21	12.55

Example 33

2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-4-chloro-phenyl ester



Initially, 14 mL of triethylamine were added dropwise to a stirred solution of 11 g (0.038 mol) of 2-(3-chloro-6-hydroxyphenyl)-5-nitrobenzimidazole in 47 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.6 g (0.038 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 4 hours. Then, 75 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the remaining liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the

solvent was removed under reduced pressure, and the product was isolated as a solid with m.p. 248-50 °C (recrystallized in ethyl acetate) with a yield of 71%.

Quantitative Analysis:

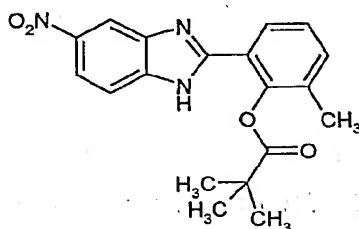
Calculated:
Found:

Calculated for $C_{18}H_{16}ClN_3O_4$

% C	% H	% N
57.84	4.31	11.24
57.87	4.35	11.08

Example 34

2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-6-methyl-phenyl ester



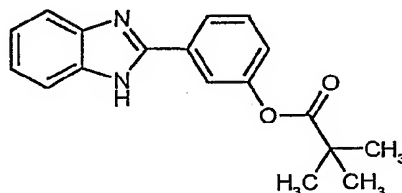
Initially, 9 mL of triethylamine were added dropwise to a stirred solution of 6.5 g (0.024 mol) of 2-(2-hydroxy-3-methyl)-5-nitrobenzimidazole in 30 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 2.91 g (0.024 mol) of 2,2-dimethylpropionyl chloride. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 8 hours. At the end, 30 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the remaining liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product isolated as a solid with m.p. 198-200°C (recrystallized in ethyl acetate) with a yield of 35%.

Quantitative Analysis:

Calculated:
Found:

Calculated for $C_{19}H_{19}N_3O_4$

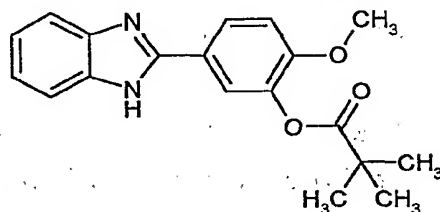
% C	% H	% N
64.58	5.42	11.89
64.76	5.46	11.86

Example 35**2,2-Dimethyl-propionic acid 5-(1H-benzimidazol-2-yl)-phenyl ester**

Initially, 17.5 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.048 mol) of 2-(3-hydroxyphenyl)benzimidazole in 60 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 5.74 g (0.048 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 14 hours. At the end, 100 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 125 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. $243-5^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 41%.

Quantitative Analysis:

	Calculated for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$		
	% C	% H	% N
Calculated:	73.45	6.16	9.52
Found:	73.80	6.51	9.39

Example 36**2,2-Dimethyl-propionic acid 3-(1H-benzimidazol-2-yl)-6-methoxy-phenyl ester**

Initially, 15 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.042 mol) of 2-(3-hydroxy-4-methoxyphenyl)benzimidazole in

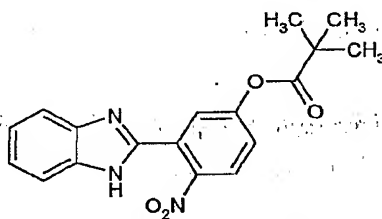
50 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 5.02 g (0.042 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 4 hours. Then, 75 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 mL). Finally, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. $202-4^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 88%.

Quantitative Analysis:

	Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$		
	% C	% H	% N
Calculated:	70.35	6.21	8.64
Found:	70.28	6.38	8.29

Example 37

2,2-Dimethyl-propionic acid 3-(1H-benzimidazol-2-yl)-4-nitro-phenyl ester



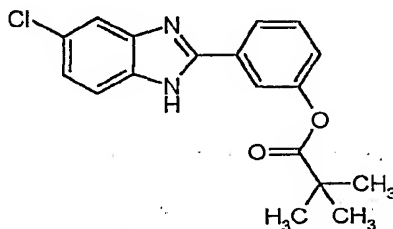
Initially, 14 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.039 mol) of 2-(5-hydroxy-2-nitro)benzimidazole in 50 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.72 g (0.039 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 4 hours. Finally, 100 mL of ethyl ether were added to the reaction mixture; the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 200 ml). The organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. $163-5^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 89%.

Quantitative Analysis:

	Calculated for $C_{18}H_{17}N_3O_4$		
	% C	% H	% N
Calculated:	63.71	5.05	12.38
Found:	63.91	5.03	12.36

Example 38

2,2-Dimethyl-propionic acid 3-(5-chloro-1H-benzimidazol-2-yl)phenyl ester



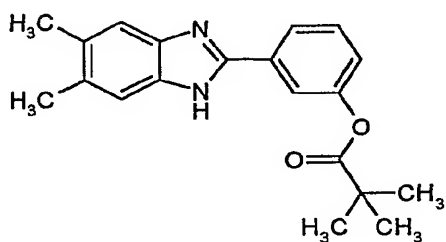
Initially, 13,5 mL of triethylamine were added dropwise to a stirred solution of 6 g (0.025 mol) of 2-(3-hydroxyphenyl)-5-chlorobenzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.44 g (0.037 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about $0^\circ C$ for 30 minutes, and then, at room temperature for 4 hours. After such a time, 45 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. = $185-7^\circ C$ (recrystallized in ethyl acetate) with a yield of 32%.

Quantitative Analysis:

	Calculated for $C_{18}H_{17}N_2O_2$		
	% C	% H	% N
Calculated:	65.75	5.21	8.52
Found:	65.58	5.07	8.44

Example 39

2,2-Dimethyl-propionic acid 3-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester



Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution composed of 8.71 g (0.037 mol) of 2-(3-hydroxyphenyl)-5,6-dimethylbenzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.4 g (0.037 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 8 hours. Finally, 75 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. $231-3^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 28%.

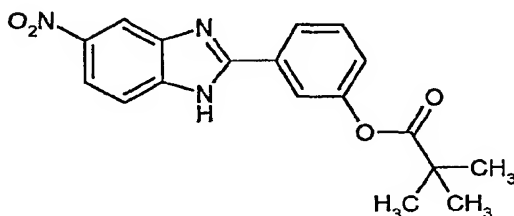
Quantitative Analysis:

Calculated:
Found:

Calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$		
% C	% H	% N
74.51	6.88	8.69
74.81	6.85	8.54

Example 40

2,2-Dimethyl-propionic acid 3-(5-nitro-1H-benzimidazol-2-yl)phenyl ester



Initially, 14 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.039 mol) of 2-(3-hydroxyphenyl)-5-nitrobenzimidazole in 47 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.72 g (0.039 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 4 hours. After that, 75 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was isolated as a solid with m.p. $201-3^\circ\text{C}$ (recrystallized in methanol) with a yield of 82%.

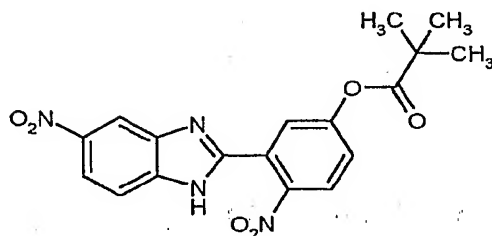
Quantitative Analysis:

Calculated:
Found:

Calculated for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$		
% C	% H	% N
63.71	5.05	12.38
64.00	5.12	12.28

Example 41

2,2-Dimethyl-propionic acid 3-(5-nitro-1H-benzimidazol-2-yl)-4-nitro-phenyl ester



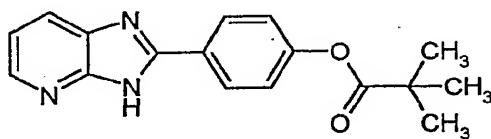
Initially, 7 mL of triethylamine were added dropwise to a stirred solution of 6 g (0.02 mol) of 2-(5-hydroxy-2-nitrophenyl)-5-nitrobenzimidazole in 25 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 2.41 g (0.02 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 4 hours. After such a time, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was obtained as a solid with m.p. $208-10^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 36%.

Quantitative Analysis:

	Calculated for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_6$		
	% C	% H	% N
Calculated:	56.25	4.20	14.58
Found:	56.42	4.17	14.53

Example 42

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester



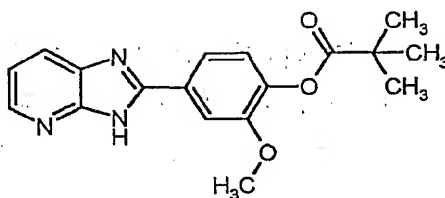
Initially, 18 mL of triethylamine were added dropwise to a stirred solution composed of 10 g (0.047 mol) of 2-(4-hydroxyphenyl)imidazo[4,5-b]pyridine in 60 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 5.71 g (0.047 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 8 hours. After such a time, 60 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. $275-7^\circ\text{C}$ (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 39%.

Quantitative Analysis:

	Calculated for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2$		
	% C	% H	% N
Calculated:	69.14	5.80	14.23
Found:	69.49	5.79	14.16

Example 43

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-b]pyridin-2-yl)-2-methoxy-phenyl ester



Initially, 16.5 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.041 mol) of 2-(4-hydroxy-3-methoxyphenyl)imidazo[4,5-b]pyridine in 55 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 4.99 g (0.041 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and, the, at room temperature for 12 hours. After that, 55 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the remainig liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over Na_2SO_4 ,

the solvent evaporated under reduced pressure, and the product obtained as a solid with m.p. 255-7°C (recrystallized in methanol) with a yield of 38 %.

Quantitative Analysis:

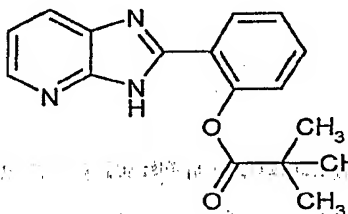
Calculated:
Found:

Calculated for $C_{18}H_{19}N_3O_3$

% C	% H	% N
66.45	5.89	12.92
66.63	6.00	12.91

Example 44

2,2-Dimethyl-propionic acid 2-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester



Initially, 18 mL of triethylamine were added dropwise to a stirred solution of 10 g (0.047 mol) of 2-(2-hydroxyphenyl)imidazo[4,5-b]pyridine in 60 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 5.71 g (0.047 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 8 hours. Finally, 60 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered and the remaining liquid was washed with H_2O (2 x 100 ml) .The organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product isolated as a solid with m.p. 162-4°C (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 81%.

Quantitative Analysis:

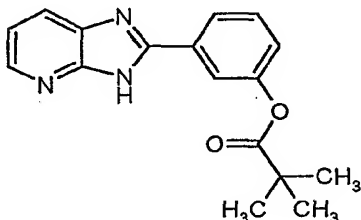
Calculated:
Found:

Calculated for $C_{17}H_{17}N_3O_2$

% C	% H	% N
69.14	5.80	14.23
69.29	5.85	14.17

Example 45

2,2-Dimethyl-propionic acid 3-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester



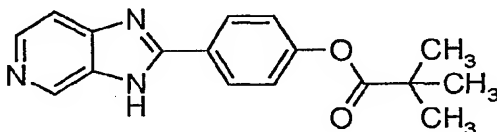
Initially, 14 mL of triethylamine were added dropwise to a stirred solution of 8 g (0.038 mol) of 2-(3-hydroxyphenyl)imidazo[4,5-b]pyridine in 48 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.57 g (0.038 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes and then, at room temperature for 9 hours. At the end, 48 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off and the liquid was washed with H_2O (2 x 200 mL). The organic phase was dried over anhydrous Na_2SO_4 , the solvent removed under reduced pressure, and the product was obtained as a solid with m.p. $204-6^\circ\text{C}$ (recrystallized in n-hexane/ethyl acetate 1:1) with a yield of 57%.

Quantitative Analysis:

	Calculated for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2$		
	% C	% H	% N
Calculated:	69.14	5.80	14.23
Found:	69.54	5.82	14.40

Example 46

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester



Initially, 10.5 mL of triethylamine were added dropwise to a stirred solution composed of 6 g (0.028 mol) of 2-(4-hydroxyphenyl)imidazo[4,5-c]pyridine in 35

mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 3.43 g (0.028 mol) of 2, 2-dimethylpropionyl chloride. Once the addition was complete, the resultant mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 12 hours. At the end, 60 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was obtained as a solid with m.p. $240-2^\circ\text{C}$ (recrystallized in ethyl acetate) with a yield of 60%.

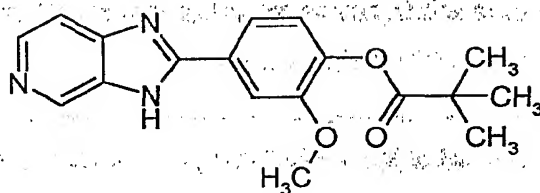
Quantitative Analysis:

Calculated:
Found:

Calculated for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2$		
% C	% H	% N
69.14	5.80	14.23
68.65	6.18	13.87

Example 47

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-c]pyridin-2-yl)-2-methoxy-phenyl ester



Initially, 15 mL of triethylamine were added dropwise to a stirred solution composed of 6 g (0.025 mol) of 2-(4-hydroxy-3-methoxyphenyl)imidazo[4,5-c]pyridine in 50 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and then, 4.49 g (0.037 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 4 hours. After such a time, 50 mL of ethyl ether were added to the mixture, the insoluble residue was filtered and the remaining liquid was washed with H_2O (2 x 100 mL). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced

pressure, and the product was obtained as a solid with m.p. 215-7°C (recrystallized in ethyl acetate) with a yield of 59%.

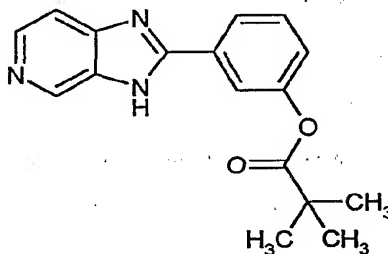
Quantitative Analysis:

Calculated:
Found:

Calculated for $C_{18}H_{19}N_3O_3$		
% C	% H	% N
66.45	5.89	12.92
66.12	5.86	12.55

Example 48

2,2-Dimethyl-propionic acid 3-(3H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester



Initially, 12.5 mL of triethylamine were added dropwise to a stirred solution of 7 g (0.033 mol) of 2-(3-hydroxyphenyl)imidazo[4,5-c]pyridine in 41 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 3.99 g (0.033 mol) of 2,2-dimethylpropionyl chloride were added. Once the addition was completed, the mixture was stirred at about 0°C for 30 minutes and next, at room temperature for 8 hours. Then, 75 mL of ethyl ether were added to the reaction mixture, the insoluble residue was filtered off and the remaining liquid was washed with H_2O (2 x 100 ml). The organic phase was dried over anhydrous Na_2SO_4 , the solvent evaporated under reduced pressure, and the product was isolated as a solid with m.p. 246-8°C (recrystallized in diisopropyl ether) with a yield of 69%.

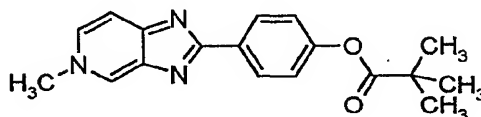
Quantitative Analysis:

Calculated:
Found:

Calculated for $C_{17}H_{17}N_3O_2$		
% C	% H	% N
69.14	5.80	14.23
68.97	5.87	14.78

Example 49

2,2-Dimethylpropionic acid 4-(5-methyl-5H-imidazo[4,5-c]pyridin-2-yl) phenyl ester.
(MAH-5)



To a stirred solution of the 2,2-dimethyl-propionic acid 4-(1H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester in acetone (20 ml) was added methyl iodide (5 ml). The mixture was stirred to reflux 18 h. Then the solvent was concentrated under reduced pressure, and the product was triturated and filtrated with EtOAc. The solid was purified by column chromatography on silica gel, eluting with CH₂Cl₂ / MeOH (10/1) to give a white solid, with a melting point of 208-209 °C. Yield: 80%.

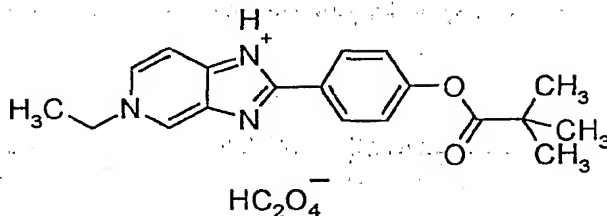
Quantitative Analysis

Calculated for C₁₈H₁₉N₃O₂ (309.37 g/mol) :

	%C	%H	%N
Calculated:	69.88	6.19	13.58
Found:	69.57	5.98	13.26

Example 50

2,2-Dimethylpropionic acid 4-(5-ethyl-5H-imidazo[4,5-c]pyridin-2-yl) phenyl ester, hydrogen oxalate. (MAH-9)



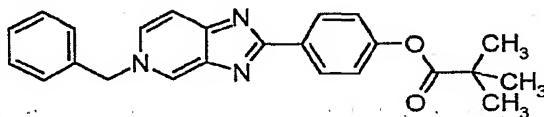
To a stirred solution of the 5-ethyl-2-(4-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridin-5-ium bromide (0.80 g, 2.2 mmol) and NaOH (0.44 g, 10.9 mmol) in dry CH₂Cl₂ (50 mL) at room temperature was added pivaloyl chloride (0.52 g, 4.4 mmol). The mixture was stirred for 5 h and then H₂O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂

(2x25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with CH_2Cl_2 / MeOH (20/1) to give an oil, which was isolated as oxalate. The salt was recrystallized from EtOH, giving a melting point of 198-199 °C. Yield: 62%

<u>Quantitative Analysis:</u>	Calculated for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_6$ (413.43 g/mol):		
	%C	%H	%N
Calculated:	61.01	5.61	10.16
Found:	60.89	5.56	10.32

Example 51

2,2-Dimethylpropionic acid 4-(5-benzyl-5H-imidazo[4,5-c]pyridin-2-yl)phenyl ester.
(MAH-6)

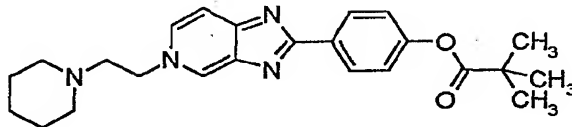


To a stirred solution of the 2,2-dimethyl-propionic acid 4-(1H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester in acetone (20 ml) was added methyl iodide (5 ml). The mixture was stirred to reflux 18 h. Then, the solvent was concentrated under reduced pressure, and the product was triturated and filtrated with EtOAc. The solid was purified by column chromatography on silica gel, eluting with CH_2Cl_2 / MeOH (10/1) to give a white solid, with a melting point of 227-228 °C. Yield: 80%.

<u>Quantitative Analysis:</u>	Calculated for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_2$ (385.47 g/mol) :		
	%C	%H	%N
Calculated:	74.78	6.01	10.90
Found:	74.59	6.09	10.96

Example 52

2,2-Dimethylpropionic acid 4-[5-(2-piperidin-1-yl ethyl)-5H-imidazo[4,5-c]pyridin-2-yl] phenyl ester. (MAH-11)



To a stirred solution of the 5-(2-piperidin-1-yl-ethyl)-2-(4-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridin-5-ium bromide (2.0 g, 6.2 mmol) and NaOH (1.25 g , 30.9 mmol) in dry CH₂Cl₂ (50 mL) at room temperature was added pivaloyl chloride (1.52 g, 12.4 mmol). The mixture was stirred for 5 h and then H₂O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x25 ml). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel , eluting with acetone / MeOH (10/1) to give a white solid, which was recrystallized from Et₂O, giving a melting point of 207-208 °C. Yield: 36%

Quantitative Analysis: Calculated for C₂₄H₃₀N₄O₂ (406.53 g/mol):

	%C	%H	%N
Calculated:	70.91	7.44	13.78
Found:	70.65	7.42	13.97

Example 53

2,2-Dimethylpropionic acid 4-[5-(2-piperidin-1-yl propyl)-5H-imidazo[4,5-c]pyridin-2-yl] phenyl ester, dihydrogen oxalate. (MAH-12)



4-(imidazo[4,5-c]pyridin-2-yl)phenol (0.5 g, 2.36 mmol) and 1-(3-iodopropyl)piperidine (0.9 g, 3.55 mol) in CH₃CN at reflux was stirred for 24 h. Then the mixture was concentrated under reduced pressure. To a stirred solution of the residue and NaOH (0.47 g, 11.8 mmol) in dry CH₂Cl₂ (50 mL) at room temperature was added pivaloyl chloride (0.28 g, 4.72 mmol). The mixture was stirred for 24 h and then H₂O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x25 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with acetone / MeOH (10/1) to give a colourless oil, which was isolated as oxalate. The salt was recrystallized from EtOH, giving a melting point of 189-190 °C. Yield: 19%

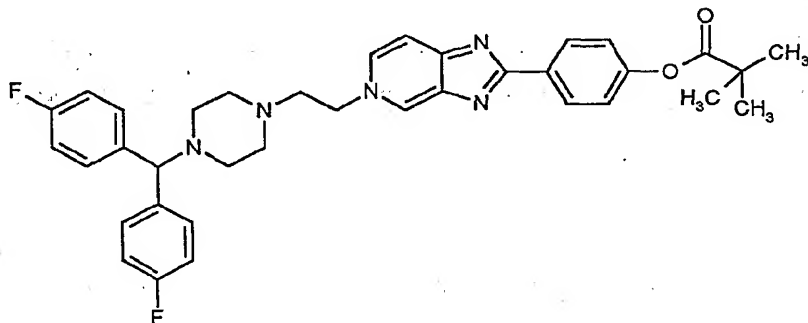
Quantitative Analysis: Calculated for C₂₉H₃₆N₄O₁₀ (600.63 g/mol):

	%H	%C	%N
Calculated	6.04	57.99	9.33
Found:	5.78	57.72	9.58

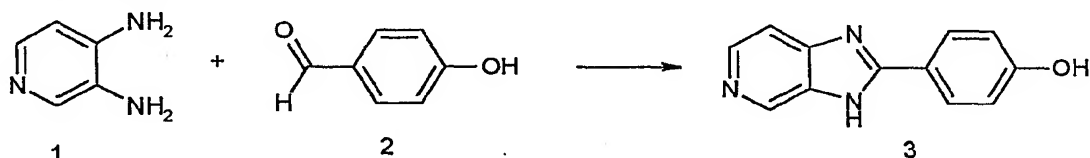
As examples 54 and 55 are more elaborated, and not simply obtained from the phenolic precursor, the full synthesis is described for both compounds:

Example 54

2, 2-dimethylpropionic acid 4-[5-(3-[4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl]-ethyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl-ester (**12**).



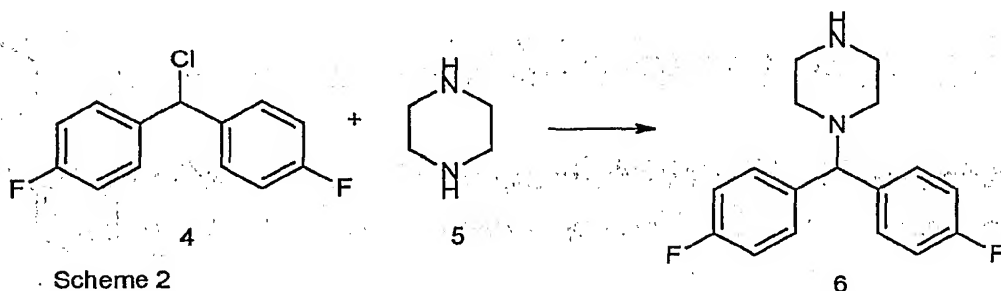
1) 4-(3H-Imidazo[4,5-c]pyridin-2-yl)-phenol (**3**)(Scheme 1). To equivalent amounts (500mg, 4.58 mmol) of 3,4-diaminopyridine and 4-hydroxybenzaldehyde (559mg)



Scheme 1

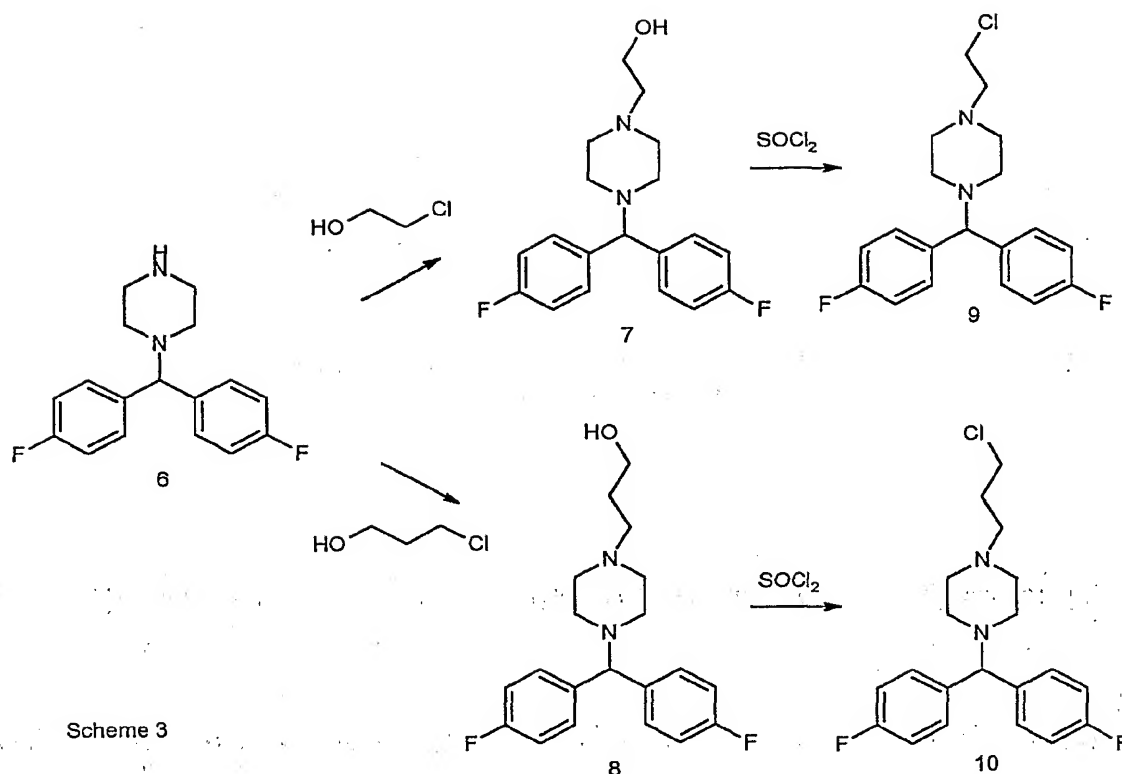
in MeOH (10 mL), SiO_2 (2.5g) was added. The solvent was evaporated to dryness and the resultant mixture was subjected to microwave irradiation in a domestic microwave oven for ten minutes (550W). The product was purified by silica gel chromatography, being eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (8:2). Compound 3 was obtained as a yellow solid (73%) with a m.p.= 246-8 °C

2) 1-[bis-(4-fluorophenyl)-methyl]-piperazine (**6**)(Scheme 2). To a stirred solution of



Scheme 2

4 (480mg, 2 mmol) in DMSO (10 mL), piperazine **5** (860mg, 10 mmoles) and KI (100mg, 0.5 mmol) in the same solvent (10 mL) was added. Triethylamine (1.4ml, 10 mmol) was added dropwise and the mixture was refluxed for 48 hours. The reaction mixture is poured into saturated solution of NaHCO_3 and extracted with ether (3x50 mL). The combined organic phases were dried over Na_2SO_4 , filtered, and evaporated to dryness. The product was purified by silica gel chromatography, being eluted with hexane/ether (3:1) yielding the compound **6** like a white solid (86%) with a m.p = 90-1°C (Lit. 90-93 °C; S. Gubert, M. Brasó, A. Sacristan, J. Ortiz; *Arzneim. Forsh.* 1987,,37(II), 1103)



Scheme 3

3) 2-(4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl)-ethanol (7)(Scheme 3). To a stirred solution of **6** (200mg, 0.69mmol) in acetonitrile (5mL), K₂CO₃ (143mg, 1.03 mmol) was added. Afterwards, 2-bromoethanol (94.9mg, 0.76 mmol) was added dropwise. The mixture was refluxed for 23 hours. The inorganic precipitate was filtered off and the solvent evaporated to dryness. The product was purified by silica gel chromatography, being eluted with ethyl acetate/methanol (4:1) yielding the compound **7** (72%) as a yellow oil.

4) 1-[Bis-(4-fluoro-phenyl)-methyl]-4-(2-chloroethyl)-piperazine (9)(Scheme 3). The compound **7** (3.44g, 10.35 mmol) in thionyl chloride (3.69g, 31.05 mmol) was refluxed for 1/2 hour. The reaction mixture was made basic with NaOH (10%) and extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and evaporated to dryness. The product was purified by silica gel chromatography, being eluted with ethyl acetate to afford **9** (85 %) as an oil.

5) 4-[5-(2-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-ethyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenol (**11**)(Scheme 4). Equivalent amounts (8.63 mmol) of compound **3** (1.82g) and compound **9** (3.03g) were dissolved in DMF (90 mL). The reaction mixture was refluxed for 19 hours. The organic solvent was evaporated to dryness. Purification of the reaction mixture by column chromatography on silica gel (ethyl acetate/methanol 4:1) yielded compound **11** in 44% yield as a yellow solid with a m. p.= 176-7°C.

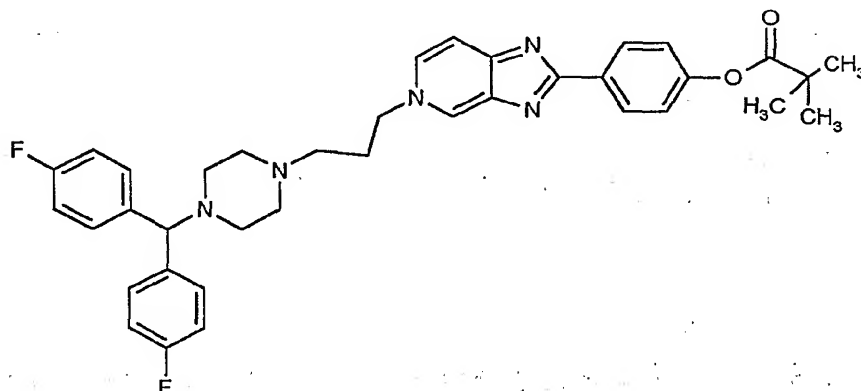
<u>Quantitative Analysis:</u>	Calculated for $C_{36}H_{37}N_2O_2F_2$		
	% C	% H	% N
Calculated:	76.17	6.57	4.93
Found:	76.34	6.37	4.71

6) 4-[5-(3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-ethyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl 2, 2-dimethylpropionate.(**12**)(Scheme 4). The compound **11** (1.28g, 2.4 mmol) was dissolved in DMF (50 ml).The solution was heated at 60 °C and NaOH (0.18g, 4.5 mmol) was added. The solution was stirred a few minutes and afterwards pivaloyl chloride (0.54g, 4.5 mmol) was added dropwise. The mixture was refluxed for 18 hours. The reaction mixture was poured in water and extracted with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 , filtered and evaporated to dryness. The product was purified by silica gel chromatography (ethyl acetate/methanol 4:1). The compound **12** was isolated as hydrochloride (76%) with a m.p. = 204-6 °C.

<u>Quantitative Analysis:</u>	Calculated for $C_{31}H_{29}N_2OF_2$		
	% C	% H	% N
Calculated:	77.00	6.04	5.79
Found:	76.84	6.32	5.71

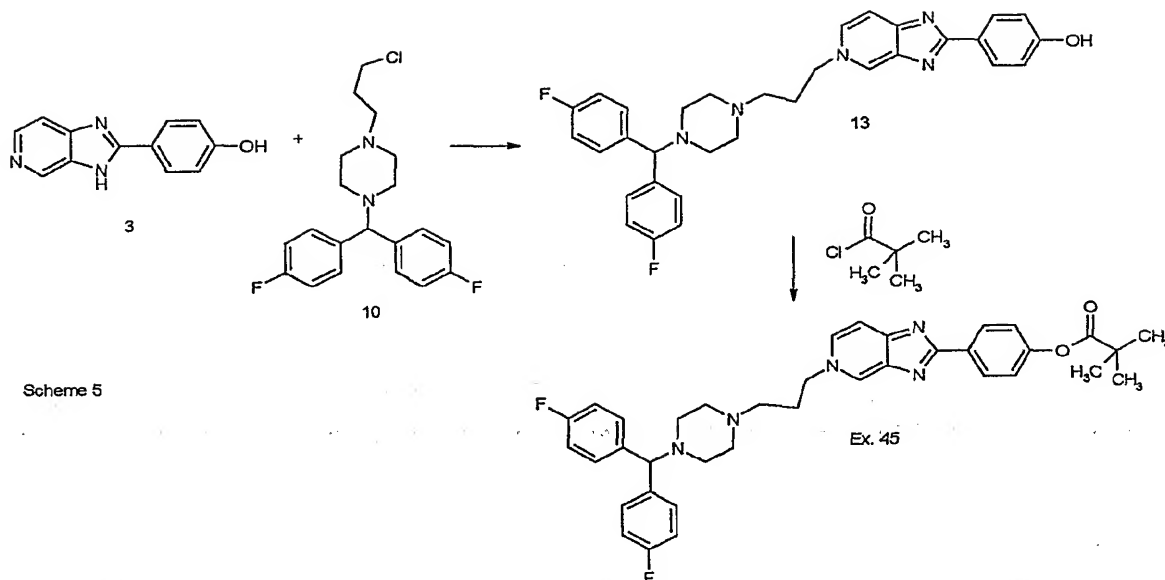
Example 55

2,2-Dimethyl-propionic acid 4-[5-(3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-propyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl ester (**14**).



1) 3-(4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl)-propan-1-ol (**8**)(Scheme 3). To a stirred solution of **6** (9.59g, 33.25 mmol) in acetonitrile (300 mL), K_2CO_3 (6.43 g, 46.55 mmol) was added. Afterwards 3-bromopropanol (5.09g, 36.6 mmol) was added dropwise. The mixture was refluxed for 15 hours. The inorganic precipitate was filtered and the organic solvent was evaporated to dryness. The product was purified by silica gel chromatography, being eluted with ethyl acetate/methanol (4:1) yielding the compound **8** (72%) as an oil.

2) 1-[Bis-(4-fluorophenyl)methyl]-4-(3-chloropropyl)piperazine (**10**)(Scheme 3). The compound **8** (8.27g, 24 mmol) in thionyl chloride (5.71g, 72 mmol) was refluxed for 1 hour. The reaction mixture was made basic with NaOH (10%) and extracted with CH_2Cl_2 . The organic phase was dried over Na_2SO_4 , filtered and evaporated to dryness. The product was purified by silica gel chromatography, being eluted with ethyl acetate to afford **10** (49 %) as an oil.



3) 4-[5-(3-[4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl]-propyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenol (**13**) (Scheme 5). The compound **3** (1.8g, 8.52 mmol) and compound **10** (3.87g, 7.17 mmol) were dissolved in DMF (80 mL). The reaction mixture was refluxed for 19 hours. The organic solvent was evaporated to dryness. Purification of the reaction mixture by column chromatography on silica gel (ethyl acetate/methanol 4:1) yielded compound **13** in 43% yield as a yellow solid with a m. p.: 240-3 °C.

Quantitative Analysis:

	Calculated for $C_{32}H_{31}N_2OF_2$		
	% C	% H	% N
Calculated:	77.24	6.28	5.63
Found:	77.34	6.17	5.84

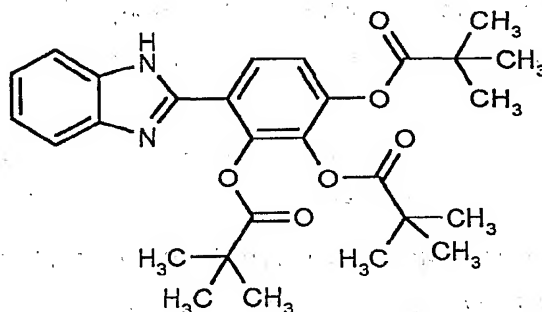
4) 2,2-Dimethyl-propionic acid 4-[5-(3-[4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl]-propyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl ester (**14**). The compound **13** (1.63g, 3.02 mmol) was dissolved in DMF (50 ml). The solution was heated at 60°C and NaOH (0.36g, 9.06 mmol) was added. The solution was stirred a few minutes and afterwards pivaloyl chloride (1.09g, 9.06 mmol) was added dropwise. The mixture was refluxed for 18 hours. The reaction mixture was poured in water and extracted with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 , filtered and evaporated to dryness. The product was purified by silica gel

chromatography, (Cl_2CH_2 /methanol 9:0.5). The compound **14** was isolated as hydrochloride. (54 %) with a m. p.= 199-201 °C.

Quantitative Analysis: Calculated for $\text{C}_{37}\text{H}_{39}\text{N}_2\text{O}_2\text{F}_2$			
	% C	% H	% N
Calculated:	76.39	6.76	4.82
Found:	76.34	6.87	4.64

Example 56

2,2-Dimethyl-propionic acid 4-(1-H-benzimidazol-2-yl)-2,3-bis-(2,2-dimethyl-propionyloxy)-phenyl ester



Initially, 13.5 mL of triethylamine were added dropwise to a stirred solution composed of 8.71 g (0.036 mol) of 2-(2,3,4-trihydroxyphenyl)benzimidazole in 45 mL of anhydrous CH_2Cl_2 , using external cooling with an ice-water bath, and next, 17.28 g (0.144 mol) of 2, 2-dimethylpropionyl chloride were added. Once the addition was completed, the resultant mixture was stirred at about 0°C for 30 minutes, and then, at room temperature for 4 hours. After that, 75 mL of ethyl ether were added to the mixture, the insoluble residue was filtered off, and the liquid was washed with H_2O (2 x 100 ml). Then, the organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure, and the product was obtained as a solid with m.p. 172-4°C (recrystallized in methanol) with a yield of 70%.

Quantitative Analysis: Calculated for $C_{28}H_{34}N_2O_6$.

	% C	% H	% N
Calculated:	68.00	6.93	5.66
Found:	68.35	6.80	5.82

Pharmacological and toxicological tests:

The pharmacological activity of the compounds of formula (I) according to the invention have been verified through the following biological tests, for some of said compounds.

The method employed was based on that described by Bieth, J., Spiess, B. and Wermuth, C.G. (1974), Biochem. Med. 11; 350-357 with some modifications.

The hydrolytic activity of HLE (Sigma, Deisenhofen, Germany) on the peptide substrate MeO-Suc-Ala-Ala-Pro-Val-p-nitroanilide (Sigma) was measured in 96-well F-bottom microliter plates. The assay buffer used consisted of 50mM Tris-HCl (pH 8) with 50mM NaCl and 0.01% Brij 35.

The enzyme (0.2 U/ml; 50 μ l) was preincubated for 15 min at room temperature in the presence of test compounds or vehicle (DMSO) in a total volume of 100 μ l.

The reaction was started by addition of 50 μ l substrate (0.5mM) and formation of p-nitroanilid was monitored by detection at 406 nm for 10 min.

Percent inhibition of enzyme activity was calculated in comparison to the corresponding vehicle control and the results obtained are mentioned in the following Table.

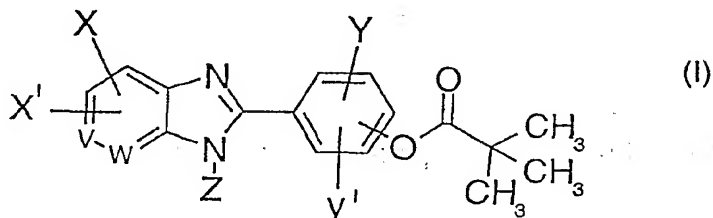
Table

Exemple n°	IC50 IN M
37	5.90 ^E -08
21	6.00 ^E -08
15	6.90 ^E -08
13	8.80 ^E -08
20	1.00 ^E -07
42	1.35 ^E -07
41	1.82 ^E -07
46	2.37 ^E -07
17	2.90 ^E -07
1	3.06 ^E -07
18	3.3 ^E -7
5	3.83 ^E -7
45	4.74 ^E -7
10	4.86 ^E -7
48	6.09 ^E -7
50	6.1 ^E -7
52	6.25 ^E -7
40	6.78 ^E -7
9	6.82 ^E -7
56	7.08 ^E -7
35	1.26 ^E -6
43	1.66 ^E -6
22	1.7 ^E -5
27	1.52 ^E -5

Regarding the toxicity it is stated that the most active compounds of formula (I) according to the invention present a low per oral toxicity with LD₅₀ more than 500 mg/kg in mice.

Claims

1. Esters of 2,2-dimethylpropionic acid having the general formula (I) :



or a pharmacological acceptable salt thereof, where

x and x' represent a hydrogen atom, an alkyl group in C1-C4, an halogen atom or a group nitro;

y and y' represent a hydrogen atom, a group alkyl in C1-C4, a group alkoxy in C1-C4, an halogen atom or a group dialkyl(C1-C4)amino;

z represents a hydrogen atom, a dialkyl(C1-C4)aminoalkyl(C1-C4) group or a piperidinyl-alkyl(C1-C4) group; and

v and w represent a carbon atom bound to a hydrogen atom (CH) or a nitrogen atom substituted or not.

2. Compounds of formula (I) according to claim 1, where

x and/or x' represent the group methyl or nitro, or a chlorine atom;

y and/or y' represent the group methyl, methoxy, nitro or diethylamino, or a chlorine, a bromine or a fluorine atom; and

z represents a group dimethylaminoethyl, dimethylaminopropyl, diisopropylaminoethyl or piperidinyl-ethyl.

3. Compounds of formula (I) according to claim 1, where v or w represents a nitrogen atom substituted by a group methyl, ethyl, benzyl, piperidiny-ethyl, piperidiny-propyl, bis(fluorophenyl)methyl-piperaziny-ethyl or bis(fluorophenyl)methyl-piperaziny-propyl.

4. The following compounds of formula (I) according to claim 1,

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-ethoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2,6-dimethoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-chloro-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-nitro-phenyl ester

2,2-Dimethyl-propionic acid 4-(1H-benzimidazol-2-yl)-2-nitro-6-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5-chloro-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-methyl-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-methyl-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5,6-dimethyl-1H-benzimidazol-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 4-(5-nitro-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 4-(5-nitro-1H-benzimidazol-2-yl)-6-methoxy-2-nitro-phenyl ester

2,2-Dimethylpropionic acid 4-[1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester.

2,2-Dimethylpropionic acid 2-bromo-4-[1-(2-dimethylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester

2,2-Dimethylpropionic acid 4-[1-(2-dimethylaminopropyl)-1H-benzimidazol-2-yl]phenyl ester, dihydrogen oxalate

2,2-Dimethylpropionic acid 4-[1-(2-diisopropylaminoethyl)-1H-benzimidazol-2-yl]phenyl ester.

2,2-Dimethylpropionic acid 4-[5,6-dichloro-1-(2-dimethylaminoethyl) 1H-benzimidazol-2-yl] phenyl ester

2,2-Dimethylpropionic acid 4-[5,6-dimethyl-3-(2-piperidin-1-yl-ethyl)-1H-benzimidazol-2-yl] phenyl ester

2,2-Dimethylpropionic acid 2-fluoro-4-[1-(2-piperidin-1-yl ethyl)-1H-benzimidazol-2-yl] phenyl ester

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-4-chloro-phenyl ester

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-5-chloro-phenyl ester

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-4,6-dichloro-phenyl ester

2,2-Dimethyl-propionic acid 2-(1H-benzimidazol-2-yl)-6-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 2-(5-chloro-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 2-(5-chloro-1H-benzimidazol-2-yl)-5-diethylamino-phenyl ester

2,2-Dimethyl-propionic acid 2-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 2-(5-methyl-1H-benzimidazol-2-yl)-4-chloro-phenyl ester

2,2-Dimethyl-propionic acid 2-(5,6-dimethyl-1H-benzimidazol-2-yl)-diethylamino-phenyl ester

2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-4-chloro-phenyl ester

2,2-Dimethyl-propionic acid 2-(5-nitro-1H-benzimidazol-2-yl)-6-methyl-phenyl ester

2,2-Dimethyl-propionic acid 5-(1H-benzimidazol-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 3-(1H-benzimidazol-2-yl)-6-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 3-(1H-benzimidazol-2-yl)-4-nitro-phenyl ester

2,2-Dimethyl-propionic acid 3-(5-chloro-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 3-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 3-(5-nitro-1H-benzimidazol-2-yl)phenyl ester

2,2-Dimethyl-propionic acid 3-(5-nitro-1H-benzimidazol-2-yl)-4-nitro-phenyl ester

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-b]pyridin-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 2-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 3-(3H-imidazo[4,5-b]pyridin-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester

2,2-Dimethyl-propionic acid 4-(3H-imidazo[4,5-c]pyridin-2-yl)-2-methoxy-phenyl ester

2,2-Dimethyl-propionic acid 3-(3H-imidazo[4,5-c]pyridin-2-yl)-phenyl ester

2,2-Dimethylpropionic acid 4-(5-methyl-5H-imidazo[4,5-c]pyridin-2-yl) phenyl ester.

2,2-Dimethylpropionic acid 4-(5-ethyl-5H-imidazo[4,5-c]pyridin-2-yl) phenyl ester, hydrogen oxalate

2,2-Dimethylpropionic acid 4-(5-benzyl-5H-imidazo[4,5-c]pyridin-2-yl)phenyl ester

2,2-Dimethylpropionic acid 4-[5-(2-piperidin-1-yl ethyl)-5H-imidazo[4,5-c]pyridin-2-yl] phenyl ester

2,2-Dimethylpropionic acid 4-[5-(2-piperidin-1-yl propyl)-5H-imidazo[4,5-c] pyridin-2- dihydrogen oxalate yl] phenyl ester

2, 2-dimethylpropionic acid 4-[5-(3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-ethyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl-ester

2,2-Dimethyl-propionic acid 4-[5-(3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-propyl)-5H-imidazo[4,5-c]pyridin-2-yl]-phenyl ester

2,2-Dimethyl-propionic acid 4-[(1-H-benzimidazol-2-yl)-2,2-dimethyl-propionyloxy]-phenyl ester

5. Esters of 2,2-dimethylpropionic acid having the general formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, as having an inhibitory activity of elastase.

6. Pharmaceutical compositions containing at least one ester of 2,2-dimethylpropionic acid of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof.

7. Pharmaceutical compositions according to claim 6, in which the quantity of ester of formula (I) is such that the dose level to be administered is comprised between 0,001 and 10 mg/kg.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 01/00327

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/12 C07D471/04 A61K31/4184 A61K31/4188
/(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 94 01455 A (ZENECA LTD) 20 January 1994 (1994-01-20) the whole document ---	1-7
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	JP 2000 273088 A (NIPPON SODA CO LTD) 3 October 2000 (2000-10-03) the whole document -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IB91/00327

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CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: NOVEL ANTI-INFECTIVES

(57) Abstract: Novel anti-infectives and methods of using them are provided.

WO 01/85172 A1

NOVEL ANTI-INFECTIVES

FIELD OF THE INVENTION

The present invention relates to novel anti-infectives. Specifically, the
5 present invention involves novel HCV inhibitors.

BACKGROUND OF THE INVENTION

First identified by molecular cloning in 1989 (Choo *et al.*, 1989), hepatitis C virus (HCV) is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo *et al.*, 1989). Due to its genome
10 structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family, along with the other two genera, flaviviruses (such as yellow fever virus and Dengue virus types 1-4) and pestiviruses (such as bovine viral diarrhea virus, border disease virus, and classic swine fever virus) (Choo *et al.*, 1989; Miller and Purcell, 1990). Like the other members of the *Flaviviridae*, HCV
15 is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome (see Figure 1) is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang and Siddiqui, 1995). This element is followed by a region which encodes a single long open
20 reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins (see Figure 2.1). This large polypeptide is subsequently processed into the individual structural and
25 nonstructural proteins by a combination of host and virally-encoded proteinases (reviewed in Rice, 1996). Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the
30 "3' X-tail" (Kolykhalov *et al.*, 1996; Tanaka *et al.*, 1995; Tanaka *et al.*, 1996; Yamada *et al.*, 1996). The 3' NTR is predicted to form a stable secondary structure

which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

Infection with HCV is a major cause of human liver disease throughout the world with seroprevalence in the general population ranging from 0.3 to 2.2% (van der Poel *et al.*, 1994) to as high as ~10-20% in Egypt (Hibbs *et al.*, 1993). HCV is most commonly transmitted via blood (Alter *et al.*, 1993). Of these initial infections, an estimated 30% are symptomatic. However, more than 85% of all infected individuals become chronically infected (3.9 million current chronic infections in US, 170 million chronic infections worldwide, estimated 33,200 new cases in 1994 in US). Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. Of the total chronic cases in the US, greater than 118,000 will go on to develop hepatocellular carcinoma (HCC) (which represents $\geq 25\%$ of all liver cancers) as a direct result of HCV infection (reviewed in Hoofnagle, 1997; Seeff, 1997). There are 8,000-12,000 deaths per year in the US currently attributed to HCV infection, and treatment costs were estimated at 600 million for 1992 in the US. The CDC estimates that the number of deaths due to HCV will increase to 38,000/yr. by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Although initially therapy consisted of interferon alone, combination therapy of interferon alpha-2b (\bullet -IFN, 3 million units injected subcutaneously three times weekly) with ribavirin (1-1.2 gms twice daily orally) for either 24 or 48 weeks is currently the most efficacious approved therapy for the treatment of chronic HCV infection. Schering-Plough alone reported over \$430 million in sales for interferon alone in 1998 specifically for HCV therapy. The response and sustained response rates for combination therapy were better than interferon alone (80% initial response for combo vs. 46% for IFN alone; and 30-50% sustained response for combo vs. 5-13% for IFN alone). However, there were still many adverse side effects associated with combination therapy (flu-like symptoms, leukopenia, thrombocytopenia, depression, etc. from interferon), as well as anemia induced by ribavirin (reviewed in Lindsay,

1997). Furthermore, this therapy was still less effective against infections caused by HCV genotype 1 which constitutes ~75% of all HCV infections in the developed markets (as opposed to other HCV genotypes). Analogous to therapy for HIV infection, combination therapy (i.e. IFN plus antiviral or antiviral cocktail) is likely to be the most efficacious therapy.

In the US, an estimated 3.9 million Americans are infected with HCV. Although only 30% of acute infections are symptomatic, >85% of infected individuals develop chronic, persistent infection. There are 8,000-10,000 deaths per year in the US currently attributed to HCV infection, and treatment costs are estimated at >600 million/yr. (1992 CDC estimate for US). Worldwide over 170 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. A vaccine is unlikely due to hypervariable surface antigens and demonstrated specificity of immunity.

Currently, there are no HCV antiviral agents available, with alpha-interferon (alone or in combination with ribavirin) being the only approved treatment. Many adverse side effects are associated with therapy (flu-like symptoms, leukopenia, thrombocytopenia, depression, anemia, etc.); only ~50-80% of the patients respond (reduction in serum HCV RNA levels, normalization of liver enzymes); however, of those treated, 50-70% relapse within 6 months of cessation of therapy.

The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens *et al.*, 1996), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intratypically (one type 1b isolate vs. another type 1b isolate, ~95-98% aa identity) and intertypically (type 1a vs. type 1b, ~85% aa identity). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.* abstract, 1999) and inhibition of NS5B RdRp activity is therefore predicted to be antiviral for HCV infection, and inhibition of RNA replication would be expected to cure infection.

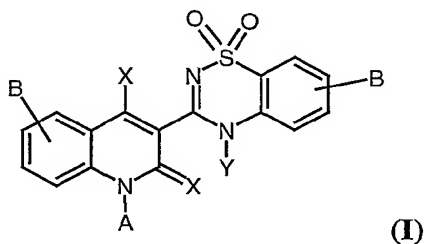
Based on the foregoing, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit HCV.

SUMMARY OF THE INVENTION

The present invention involves compounds represented hereinbelow, pharmaceutical compositions comprising such compounds and methods of using the present compounds.

5 DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present methods are selected from Formula (I) hereinbelow:



10

wherein:

A is selected from the group consisting of C 1-6 alkyl, C 2-6 alkenyl, alkylaryl, aryl, and heteroaryl;

15 B is selected from one or more of the group consisting of H, C 1-6 alkyl, C 1-6 cycloalkyl, halo, OR1, COR1, COOR1, CONR1R2, and CN wherein R1 and R2 are, independently, H, C 1-6 alkyl, aryl and heteroaryl;

X is selected from the group consisting of O, OR1, S, and SR1 wherein R1 is as defined above; and

20 Y is selected from the group consisting of H, C 1-6 alkyl, alkylaryl, aryl, and heteroaryl.

Preferably, A is selected from the group consisting of C 1-6 alkyl, and alkylaryl;

Preferably, B is H.

Preferably, X is selected from the group consisting of OH, and SH.

Preferably, Y is hydrogen.

25 As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined together by single carbon-carbon bonds. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. "Aryl" includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. Preferred aryl
5 moieties are phenyl, unsubstituted, monosubstituted, disubstituted or trisubstituted. Preferred heteroaryl moieties are selected from the group consisting of unsubstituted, monosubstituted, disubstituted or trisubstituted thienyl, quinolinyl, indolyl and pyridinyl. Preferred aryl and heteroaryl substituents are selected from the group consisting of C 1-4 alkyl, NC 1-4 alkyl, halo, OC1-4 alkyl, CH=CH, CF₃, pyridine,
10 phenyl, NO₂, CN, OH and MeO.

More preferably, alkyl substituents are methyl or ethyl. More preferably, halo substituents are chloro or bromo.

Preferred compounds useful in the present invention are selected from the group consisting of:

1-(n-Propyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-(n-Butyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-Benzyl-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-(2-Pyridylmethyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-(3-Cyanopropyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-[(3-Methyl)butyl]-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

1-[(2-Methyl)propyl]-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

1-(4-Cyanobutyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

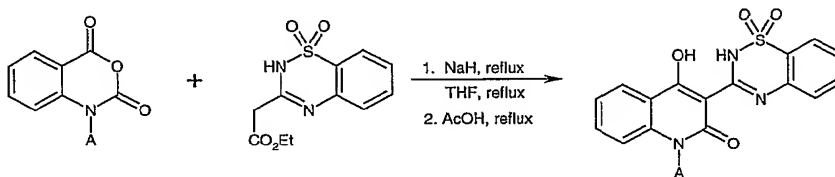
1-(n-Pentyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone; and

1-(2-Butenyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone.

1-(2-Propenyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone.

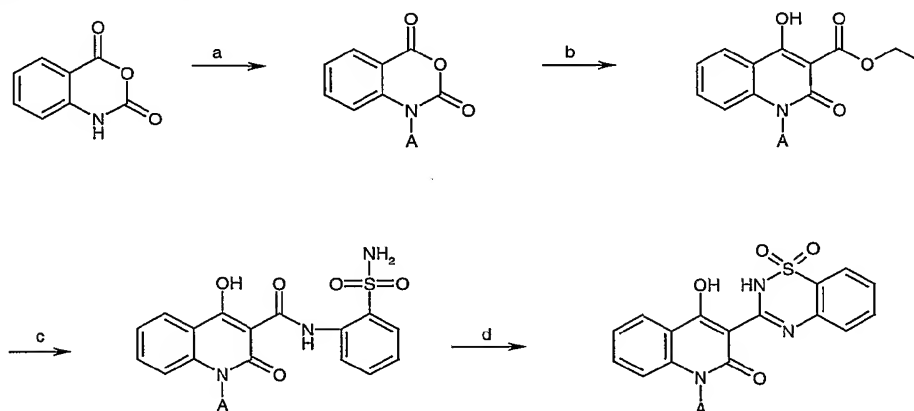
Also included in the present invention are pharmaceutically acceptable salt complexes. Preferred are the ethylene diamine, sodium, potassium, calcium, ethanolamine, hydrochloride, hydrobromide and trifluoroacetate salts.

Also included in the present invention is a process according to Scheme 1 for the synthesis of the compounds :



Scheme 1

Also included in the present invention is a process according to Scheme 2 for the synthesis of the compounds :



Conditions: a) Sodium hydride / A-Cl / DMA; b) Sodium hydride / diethylmalonate / DMA; c) 2-Aminobenzenesulfonamide / toluene; d) Sodium hydroxide / reflux.

15

Scheme 2

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

Example 1

1-(3-Cyanopropyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

a) N-(3-cyanopropyl)isatoic anhydride

Isatoic anhydride (1.63 g, 10.0 mmol) was added to a stirred mixture of 4-bromobutyronitrile (2.96 g, 20.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and dimethylformamide (15 mL) and stirring continued for 5 h. The mixture was poured into water and extracted with ethyl acetate. The extracts were washed with water, saturated aqueous NaCl, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue chromatographed (silica gel, 50-70% ethyl acetate/hexane) to give the title compound (187 mg, 8%) as a gum.

b) 1-(3-Cyanopropyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

Sodium hydride (60 mg of a 60% oil dispersion, 1.50 mmol) was added to a stirred solution of N-(3-cyanopropyl)isatoic anhydride (86 mg, 0.373 mmol) and ethyl 1,1-dioxo-2H-benzo-1,2,4-thiadiazinyl-3-acetate (100 mg, 0.373 mmol, lit. ref.: Kovalenko, S. N.; Chernykh, V. P.; Shkarlat, A. E.; Ukrainets, I. V.; Gridasov, V. I.; Rudnev, S. A., *Chem.Heterocycl.Comp.d.(Engl.Transl.)*, 1998, 34(7), 791) in tetrahydrofuran (3 mL) at room temperature under argon. After 5 min, the mixture was stirred under reflux for 2.5 h, then cooled and acetic acid (1 mL) added. The mixture was heated again under reflux for 1 h, then cooled, poured into aqueous hydrochloric acid and cooled in ice. The precipitate was filtered, washed with water and air-dried. The solid was reprecipitated from tetrahydrofuran/water to give the title compound (100 mg, 66%) as a pale yellow solid. LCMS m/z 409 [M+H]⁺.

Example 2

3-(1,1-Dioxo-1,4-dihydro-1,6-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-pyridin-2-ylmethyl-1 H-quinolin-2-one

a) 1-Pyridin-2-ylmethyl-1 H-benzo[d][1,3]oxazin-2,4-dione

To a suspension of isatoic anhydride (1.63 g, 10 mmol) in anhydrous dimethylacetamide (10 ml) was added sodium hydride (0.44 g, 11 mmol, 60% oil

dispersion) in portions. After stirring at room temperature for 30 minutes, 2-chloromethylpyridine [prepared from treatment of a suspension of 2-picoly chloride hydrochloride (2.16 g, 13.17 mmol) with aqueous base, drying (MgSO₄) and subsequent evaporation of organic solvent] was added and stirring continued for 48
5 hrs. The mixture was poured into iced water (100 ml), stirred vigorously for 30 minutes and the resulting brown solid filtered off. After air-drying, the yield was 1.05 g, 41%. MS (ES+) m/e 255 [M+H]⁺, and 509 [2M+H]⁺.

b) 4-Hydroxy-2-oxo-1-pyridin-2-ylmethyl-1,2-dihydroquinolin-3-carboxylic acid ethyl ester

10 Sodium hydride (0.33 g, 8.27 mmol, 60% oil dispersion) was washed with *n*-hexane (2 x 25 ml), dried off *in vacuo*, and re-suspended in anhydrous dimethylacetamide (5 ml). This suspension was stirred and treated portion-wise with diethyl malonate (1.32 g, 8.27 mmol) in anhydrous dimethylacetamide (5 ml) at room temperature. After 15 minutes, a solution of 1-pyridin-2-ylmethyl-1 *H* –
15 benzo[d][1,3]oxazin-2,4-dione (1.05 g, 4.13 mmol) was added over 2 minutes and the mixture warmed to 120°C. After another 2 hrs. the mixture was cooled, concentrated to a quarter of the original volume. The residue was partitioned between dichloromethane (25 ml) and water (20 ml), the aqueous phase separated, washed with more dichloromethane (4 x 25 ml), and acidified. The aqueous phase
20 was extracted with fresh dichloromethane (3 x 25 ml), combined organic extracts dried (MgSO₄) and evaporated to afford a solid (0.86 g) which was washed successively with ethanol and diethyl ether to give the title compound as pale brown crystals (0.37 g, 28%). ¹H NMR (CDCl₃) – 14.4 (1H, s), 8.6 (1H, m), 8.2 (1H, dd), 7.5 – 7.6 (2H, m), 7.4 (1H, d), 7.1 – 7.3 (together 3H, m), 5.6 br (2H, s), 4.55 (2H,
25 q), and 1.65 (2H, t), MS (ES+) m/e 325 [M+H]⁺, and 671 [2M+H]⁺.

c) 4-Hydroxy-2-oxo-1-pyridin-2-ylmethyl-1,2-dihydroquinolin-3-carboxylic acid (2-sulfamoylphenyl)-amide

4-Hydroxy-2-oxo-1-pyridin-2-ylmethyl-1,2-dihydroquinolin-3-carboxylic acid ethyl ester (213 mg, 0.657 mmol) was dissolved in toluene (10 ml) at 50°C and
30 2-aminobenzenesulfonamide (113 mg, 0.656 mmol) added. The resulting mixture was heated under reflux for 18 hrs., cooled to room temperature and the solid formed

filtered off. After washing well with diethyl ether the solid was dried *in vacuo* (290 mg, 98%). MS (ES+) m/e 451 [M+H]⁺, and 901 [2M+1]⁺.

d) 3-(1,1-Dioxo-1,4-dihydro-1*H*-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1-pyridin-2-ylmethyl-1*H*-quinolin-2-one

5 4-Hydroxy-2-oxo-1-pyridin-2-ylmethyl-1,2-dihydroquinolin-3-carboxylic acid (2-sulfamoylphenyl)-amide (115 mg, 2.3 mmol) was dissolved in 10% aqueous NaOH (4 ml), water (10 ml) added and the resulting solution heated under reflux for 2 days. After cooling, the solution was filtered, filtrate acidified and the milky solution filtered. The solid thus obtained was heated in DMSO (2 ml) and the hot
10 suspension filtered. The filtrate was purified by preparative HPLC to give the title compound (20 mg, 18%). ¹H NMR (DMSO) 15.4 br(1H,s), 14.25br (1H, s), 8.5 (1H, d), 8.25 (1H, d), 7.95 (1H, d), 7.75-7.85 (together 3H, m), 7.7 (1H, d), 7.5 – 7.6 (together 2H, m), 7.45 (1H, t), 7.35 (1H, d), 7.3 (1H, m), and 5.75 (2H, s). MS (ES+) m/e 433 [M+H]⁺.

15

Example 3

1-Benzyl-3-(1,1-dioxo-1,2-dihydro-1*H*-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-quinolin-2-one

Following the procedure of Example 2(a), 1(b), 1(c) and 1(d), except substituting benzyl bromide for 2- chloromethylpyridine, the title compound was
20 prepared as a white crystalline solid. MS (ES+) m/e 432 [M+H]⁺.

Example 4

1-Butyl-3-(1,1-dioxo-1,2-dihydro-1*H*-benzo[1,2,4]thiadiazin-3-yl)-4-hydroxy-1*H*-quinolin-2-one

Following the procedure of Example 1(a), 1(b), 1(c) and 1(d), except
25 substituting *n*-butyl bromide for 2- chloromethylpyridine, the title compound was prepared as a white crystalline solid. MS (ES+) m/e 398 [M+H]⁺, 795 [2M+1]⁺, and 1214 [3M+Na]⁺.

Example 5

30 1-[(3-Methyl)butyl]-3-(1,1-dioxo-2*H*-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

Following the procedure of Example 2(a) and 1(b), except substituting 3-methyl-1-bromobutane for 2-chloromethylpyridine, the title compound was prepared as a pale yellow solid after recrystallization. MS (ES+) m/e 412 [M+H]⁺.

Example 6

5 **1-(4-Cyanobutyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone**

Following the procedure of Example 2(a) and 1(b), except substituting 4-cyano-1-bromobutane for 2-chloromethylpyridine, the title compound was prepared as a white crystalline solid after recrystallization. MS (ES+) m/e 423 [M+H]⁺.

10 **Example 7**

1-(2-Butenyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

Following the procedure of Example 2(a) and 1(b), except substituting (E)-1-bromo-2-butene for 2-chloromethylpyridine, the title compound was prepared as a pale yellow solid after recrystallization. MS (ES+) m/e 396 [M+H]⁺.

15 **Example 8**

1-[(2-Methoxy)ethyl]-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

Following the procedure of Example 2(a) and 1(b), except substituting 1-bromo-2-methoxy-ethane for 2-chloromethylpyridine, the title compound was prepared as a pale yellow solid after recrystallization. MS (ES+) m/e 400 [M+H]⁺.

Example 9

1-(n-Propyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

Following the procedure of Example 2(a) and 1(b), except substituting 1-bromopropane for 2-chloromethylpyridine, the title compound was prepared as a white solid after recrystallization. MS (ES+) m/e 384 [M+H]⁺.

Example 10

1-(n-Pentyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone

Following the procedure of Example 2(a) and 1(b), except substituting 1-bromopentane for 2-chloromethylpyridine, the title compound was prepared as a pale yellow solid after recrystallization. MS (ES+) m/e 412 [M+H]⁺.

Example 11**1-[(2-Methyl)propyl]-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone**

Following the procedure of Example 2(a) and 1(b), except substituting 2-methylbromopropane for 2-chloromethylpyridine, the title compound was prepared as a solid after recrystallization. MS (ES+) m/e 398 [M+H]⁺.

Example 12**1-(2-Propenyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone**

Following the procedure of Example 2(a) and 1(b), except substituting allyl bromide for 2-chloromethylpyridine, the title compound was prepared as a solid after recrystallization. MS (ES+) m/e 382 [M+H]⁺.

Also included in the present invention are pharmaceutically acceptable salt complexes. Preferred are the ethylene diamine, sodium, potassium, calcium, ethanolamine, hydrochloride, hydrobromide and trifluoroacetate salts. The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The present ligands can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the

compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized
5 forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and
10 fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.
15 The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound (IC_{50}) potency, (EC_{50}) efficacy, and the biological half-life (of the compound), the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of
20 ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered. Oral administration is a preferred method of administration of the present compounds.

25 Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single
30 dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula(I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation, prophylaxis, therapy and cure of the disease. As used herein, "diseases" treatable using the present compounds include, but are not limited to keratitis, encephalitis, herpes labialis, neonatal disease, genital herpes, chicken pox, shingles, pneumonia, colitis, retinitis, cytomegalic inclusion disease, roseola, febrile seizures, bone marrow graft suppression, interstitial pneumonitis, multiple sclerosis, mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, Kaposi's sarcoma, and multiple myeloma.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

5 Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

10 A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

15 Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

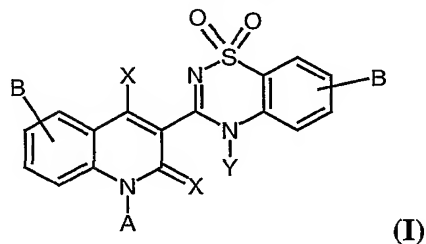
20 No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The HCV NS5B inhibitory activity of the compounds of Formula (I) was determined using standard procedures well known to those skilled in the art and described in, for example Behrens et al., EMBO J. 15:12-22 (1996) and Lohmann et al., Virology 249:108-118 (1998).

25 All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I) hereinbelow:



5

wherein:

A is selected from the group consisting of C 1-6 alkyl, C 2-6 alkenyl, alkylaryl, aryl, and heteroaryl;

B is selected from one or more of the group consisting of H, C 1-6
 10 cycloalkyl, halo, OR1, COR1, COOR1, CONR1R2, and CN wherein R1 and R2 are,
 independently, H, C 1-6 alkyl, aryl and heteroaryl;

X is selected from the group consisting of O, OR1, S, and SR1 wherein R1 is as defined
 above; and

Y is selected from the group consisting of H, C 1-6 alkyl, alkylaryl, aryl, and heteroaryl.

15

2. A compound according to claim 1 selected from the group consisting of:

1-(n-Propyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-(n-Butyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-Benzyl-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

20 1-(2-Pyridylmethyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-
 quinolone;

1-[(2-Methyl)propyl]-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-
 quinolone

1-(3-Cyanopropyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

25 1-[(3-Methyl)butyl]-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-
 quinolone;

1-(4-Cyanobutyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone;

1-(n-Pentyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone; and
1-(2-Butenyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-quinolone.
1-(2-Propenyl)-3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazin-3-yl)-4-hydroxy-2-
quinolone.

5

3. A method of treating or preventing infection which comprises administering to a subject in need thereof, an effective amount of a compound according to claim 1.

4. A method according to claim 3 which involves inhibiting HCV.

10

5. A method according to claim 3 in which the compound is administered in an oral dosage form.

6. A method of preparing a compound according to claim 1 comprising the step of
15 reacting an anhydride with an anion.

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PCT/US01/15105

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/549; C07D 417/04

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN/CAS: structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,378,704 A (WELLER, III) 03 January 1995, entire document.	1-6

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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ning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOPYRIDINE AND IMIDAZOPYRIMIDINE ANTIVIRAL AGENTS

(57) Abstract: The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides imidazopyridine and imidazopyrimidine derivatives (Formula I) for the treatment of respiratory syncytial virus infection.



WO 01/95910 A1

IMIDAZOPYRIDINE AND IMIDAZOPYRIMIDINE
ANTIVIRAL AGENTS

BACKGROUND OF THE INVENTION

5

1. **Field of the Invention**

The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections.

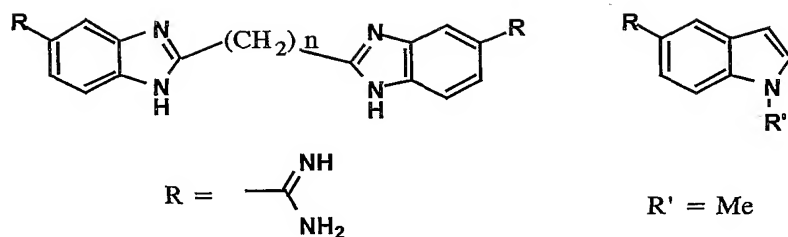
10 More particularly, the invention provides imidazopyridine and imidazopyrimidine derivatives (Formula I) for the treatment of respiratory syncytial virus infection.

2. **Background Art**

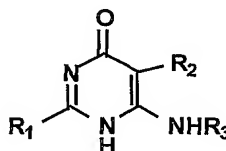
15 Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infection in infants, children, elderly and immunocompromised persons. Severe infection of the virus may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, 277, 12). Currently only Ribavirin is approved for the treatment of this viral infection.

20 Ribavirin is a nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. Other than Ribavirin, RespiGam and Synagis are an immunoglobulin and monoclonal antibody, respectively, that neutralize RSV. They are the only two biologics that have been approved for prophylactic use in high risk pediatric
25 patients for RSV infection. Both RespiGam and Synagis are very expensive and require parental administration.

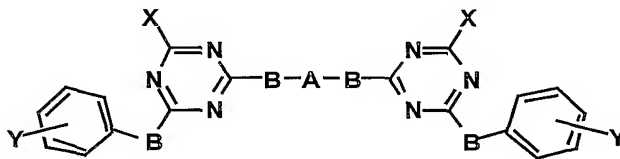
Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193). Y. Tao et al. (EP 0 058 146 A1, 1998)
30 disclosed that Cetirizine, a known antihistamine, exhibited anti-RSV activity. Tidwell et al., *J. Med. Chem.* 1983, 26, 294 (US Patent 4,324,794, 1982), and Dubovi et al., *Antimicrobial Agents and Chemotherapy*, 1981, 19, 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.



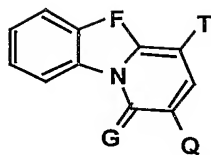
Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.



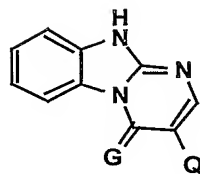
In addition, Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, 38, 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or prevention of RSV infection.



Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, 3, 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these compounds are shown in formulas Id and Ie, in which F = NH, S, or O; Q = -NHCOPh, -COOH, COOEt, or CN; T = COMe, CN, or COOEt; G = O or NH.

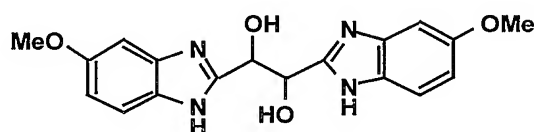


Formula Id

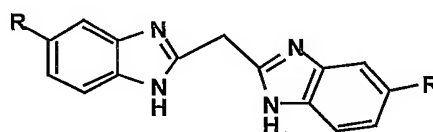


Formula Ie

A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, 15, 655).

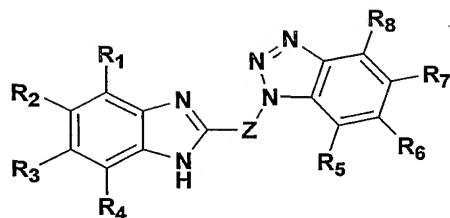


Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, 5, 71).

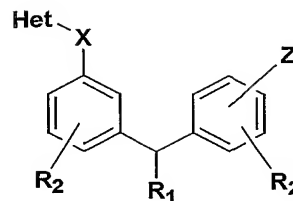


R = H, NO₂

Most recently Yu et al. have discovered a series of benzimidazoles (Formula II) for the treatment and prevention of RSV infection (WO 00/04900). In addition, Theodore Nitz has also found a series of compounds with Formula III that inhibit RSV in Hep-2 cell tissue culture assay (WO 99/38508). Although many other agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193) none of them have been used in human clinical trials. Thus, there is a medical need for a convenient and less expensive anti-viral agent for the treatment and prevention of RSV infection.



Formula II

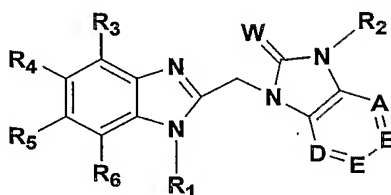


Formula III

5

SUMMARY OF THE INVENTION

This invention relates to compounds having the Formula I, and pharmaceutically acceptable salts thereof



Formula I

10

wherein:

15 W is O or S;

R₁ is -(CR'R'')_n-X;

X is H, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR''', NR'R'', NR'COR'', NR'CONR''R''', NR'SO₂R'', NR'COOR'', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', PO(OR')₂, aryl, heteroaryl or non-aromatic heterocycle;

25

m is 0-2; n is 2-6;

R₂ is

- (i) H, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, -(CH₂)_t C₃₋₇ cycloalkyl, -(CH₂)_t C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is 1-6;
- (ii) -(CR'R")_n-Y, wherein Y is CN, OR', OCONR'R", NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR'R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂; wherein m is 0-2 and n' is 1-6;
- (iii) -(CR'R")_n-C₆H₄-Z, wherein the Z group may be in the ortho, meta or para position relative to the -(CH₂)_n group; Z is CN, OR', OCONR'R", NO₂, NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR'R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂;
- m is 0-2; n" is 0-6; or
- (iv) -(CR'R")_n-heteroaryl, wherein n" is 0-6;
- (v) -(CR'R")_n-non-aromatic heterocycle, wherein n" is 0-6;
- R₃, R₄, R₅ and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkyl substituted with one to six of the same or different halogen atoms, OR', CN, COR', COOR', CONR'R", or NO₂;
- A, B, E, D are each independently C-H, C-Q-, N, or N-O; provided at least one of A, B, E or D is not C-H or C-Q; wherein Q is halogen, C₁₋₃ alkyl or C₁₋₃ alkyl substituted with one to three of the same or different halogen atoms; and

R', R'', R''' are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; or R' and R'' taken together form a cyclic alkyl group
5 having 3 to 7 carbon atoms; benzyl or aryl ;

R'''' is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, NR'R'', CR'NR''R''', aryl, heteroaryl, non-aromatic heterocycle; and

10 Non-aromatic heterocycle is a 3-7 membered non-aromatic ring containing at least one and up to 4 non-carbon atoms selected from the group consisting of O, S, N, and NR';

Aryl is phenyl, naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl;

15

Heteroaryl is a 4-7 membered aromatic ring which contains one to five heteroatoms independently selected from the group consisting of O, S, N or NR', wherein said aromatic ring is optionally fused to group B';

20 B' is an aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl;

Aryl, B', said 4-7 membered aromatic ring, and said 3-7 membered non-aromatic ring may each independently contain one to five substituents which are each

25 independently selected from R₇, R₈, R₉, R₁₀ or R₁₁; and

R₇, R₈, R₉, R₁₀ and R₁₁ are each independently

(i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; and

5 (ii) halogen, CN, NO₂, OR', NR'R'', COR', COOR', CONR'R'', OCOR', NR'COR'', SO_mR', SO₂NR'R'', PO(OR')₂.

A preferred embodiment includes compounds of Formula I wherein heteroaryl is selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, 10 pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, 15 benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, tetrazole and phenoxazinyl.

20 Another preferred embodiment includes compounds of Formula I wherein:

R₁ is -(CH₂)_n-X;

X is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, 25 each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'', NR'R'', NR'COR'', NR'COOR'', COR', CR''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', aryl or heteroaryl;

30 m is 0-2; n is 2-4;

R₂ is

(i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, -(CH₂)_t C₃₋₇ cycloalkyl, -(CH₂)_t C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of
5 the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is 1-6;

(ii) -(CH₂)_n-Y, wherein Y is CN, OR', COR', COOR', CONR'R", SO_mR', SO₂NR'R", PO(OR')₂ wherein m is 0-2 and n' is 1-6; or
10

(iii) -(CH₂)_n"-C₆H₄-Z, wherein the Z group may be in the ortho, meta or para position relative to the -(CH₂)_n" group; Z is CN, OR', COR' or SO_mR'; m is 0-2; n" is 0-3;

15 R₃, R₄, R₅, and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, optionally substituted with one to six of the same or different halogen atoms; and

A, B, E, D are each independently C-H or N; provided at least one of A, B, E or D is not C-H.

20

Another preferred embodiment includes compounds of Formula I wherein:

R₃, R₄, R₅ and R₆ are each H;

25 A, B and D are each C-H; and

E is N.

Another preferred embodiment includes compounds of Formula I wherein:

30

R₃, R₄, R₅ and R₆ are each H;

A, B and E are each C-H; and

D is N.

5 In another embodiment of the invention there is provided a method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds of having Formula I, including pharmaceutically acceptable salts thereof.

10 Another embodiment includes a pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned anti-RSV compounds having Formula I, including pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

15 The term pharmaceutically acceptable salt includes solvates, hydrates, acid addition salts and quarternary salts. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic or organic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, 20 methanesulfonic, acetic, citric, malonic, fumaric, maleic, oxalic acid, sulfamic, or tartaric acids. Quaternary salts include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, oxalate, sulfamate, and tartrate. Halogen means bromine, chlorine, fluorine and iodine.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply unless indicated otherwise:

5 An “aryl” group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl.

10 As used herein, a “heteroaryl” group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, 15 imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, and pyrazinyl.

20 As used herein, a “non-aromatic heterocycle” group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of non-aromatic heterocycle 25 groups are azetidiny, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, oxazolidonyl, oxazolonyl, 2-pyrrolidinonyl, hydantoinyl, meleimidyl and oxazolidinedionyl.

30 An “alkyl” group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., “1-20”, is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More

preferably, it is a medium size alkyl having 1 to 10 carbon atoms. For example, the term "C₁₋₆ alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

5

A "cycloalkyl" group refers to a saturated all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system.

Examples, without limitation, of cycloalkyl groups are cyclopropane,

10 cyclobutane, cyclopentane, cyclohexane, cycloheptane, and adamantane.

A "cycloalkenyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one or more rings contains one or more carbon-carbon double bonds but does not have a completely conjugated pi-electron system. Examples, without limitation, of

15

cycloalkenyl groups are cyclopentene, cyclohexadiene, and cycloheptatriene.

An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond.

20

An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an -OH group.

25

An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group as defined herein.

An "O-carboxy" group refers to a R^{''}C(O)O-group, with R^{''} as defined

30

herein.

An "amino" group refers to an -NH₂ group.

A "N-amido" group refers to a $R^x C(=O)NR^y$ - group, with R^x selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heteroalicyclic and R^y selected from hydrogen or alkyl.

5 A "cyano" group refers to a $-CN$ group.

It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well
10 understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

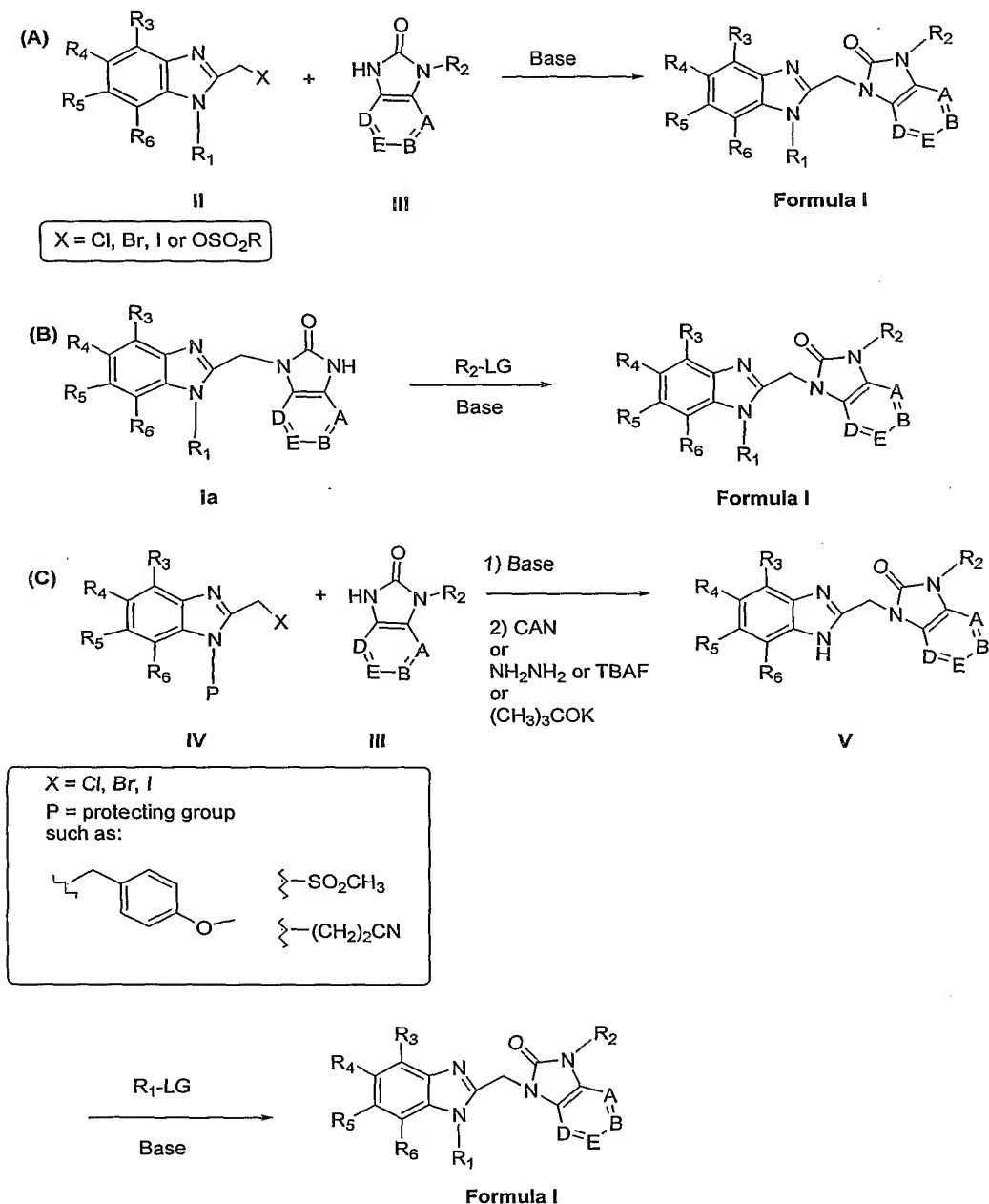
15

Compounds of Formula I can be prepared either by coupling 2-substituted-benzimidazoles (II), where X is a halide or sulfonate such as mesylate or tosylate, with 2-oxo-imidazopyridines or 2-oxo-imidazopyrimidines (III) in the presence of base, preferably phosphazene bases such as t-butyylimino-
20 tri(pyrrolidino)phosphorane (BTPP), cesium carbonate or sodium hydride (Scheme I-A) or by reacting Ia with a R_2-LG , where LG is a leaving group, preferably a halide or sulfonate such as mesylate or tosylate (Scheme I-B). Alternatively, compounds of Formula I can be synthesized according to the procedure described in Scheme I-C. Coupling of 2-substituted-benzimidazoles
25 (IV) containing protecting groups (P) such as p-methoxybenzyl, mesyl, or 2-cyanoethyl with 2-oxo-imidazopyridines or 2-oxo-imidazopyrimidines in the presence of base is followed by removal of the protecting group using appropriate conditions. Deprotection can be accomplished by treatment with ceric ammonium nitrate (CAN), treatment with hydrazine or tetrabutylammonium
30 fluoride (TBAF), or treatment with potassium *tert*-butoxide to respectively remove p-methoxybenzyl, mesyl, or 2-cyanoethyl groups and give intermediates V. Compounds of Formula I can then be prepared by reacting V with R_1-LG

where LG is a leaving group preferably a halide or sulfonate such as mesylate or tosylate.

Scheme I: Preparation of Formula I

5

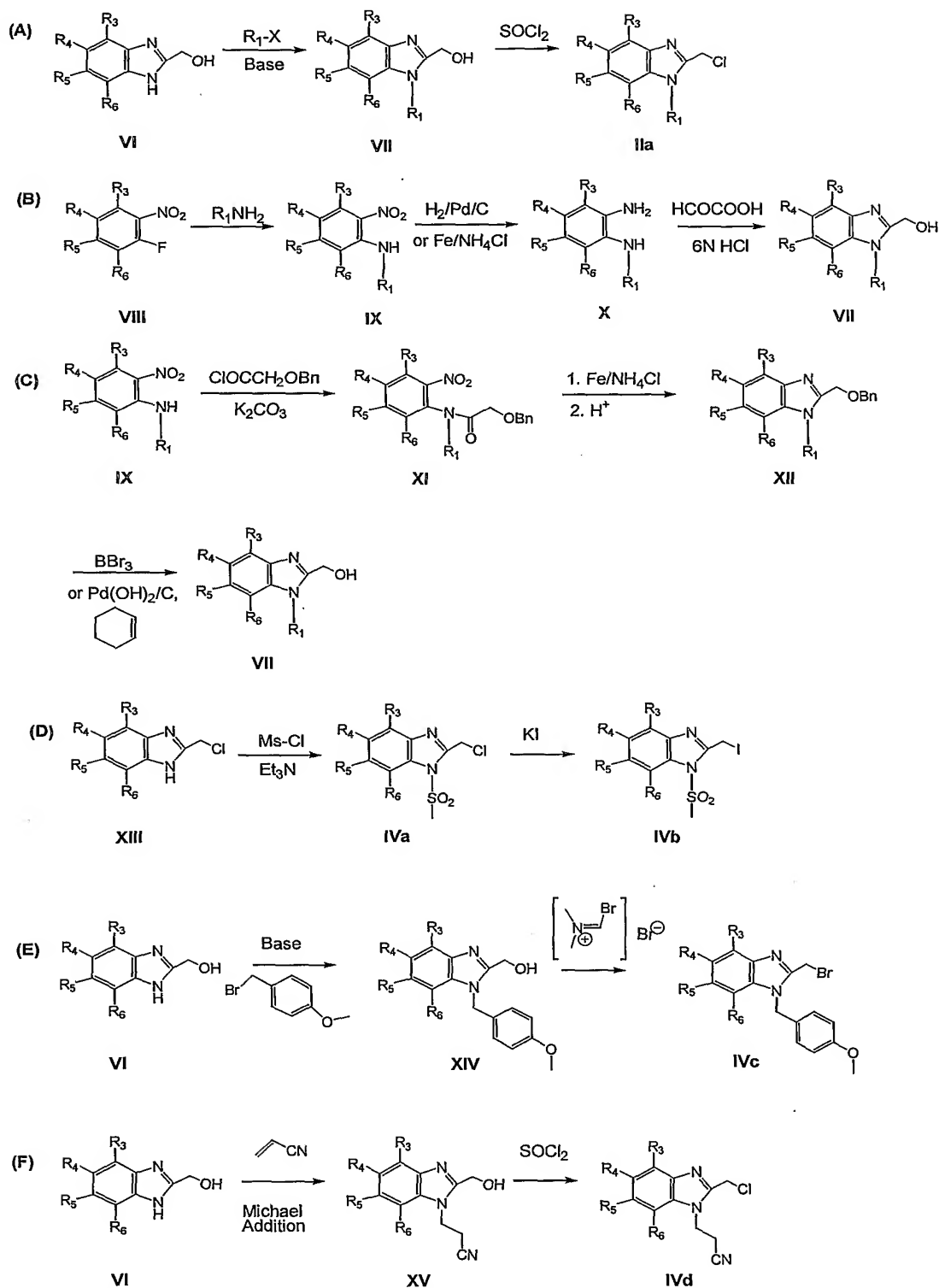


The synthesis of 2-substituted-benzimidazoles (IIa) is shown in Schemes II A-C. Treatment of substituted or unsubstituted 2-hydroxymethylbenzimidazole

- (VI) with 1.05 equivalents of base, preferably sodium hydride or cesium carbonate, followed by the addition of R₁-LG, where LG is a leaving group such as halide or sulfonate, gives compound VII. Treatment of the alcohol with thionyl chloride provides 2-chloromethyl-benzimidazole IIa (Scheme II-A). In a separate synthetic route, depicted in Scheme II-B, 2-fluoro-nitrobenzene (VIII) reacts with an amine to afford compound IX. Reduction of the nitro group provides a phenylenediamine derivative X which is cyclized with glycolic acid in 4-6 N HCl to give alcohol VII. Alternatively, 2-amino-nitrobenzene (IX) is acylated with 2-benzyloxyacetyl chloride to provide XI (Scheme II-C).
- 10 Reduction of the nitro group followed by ring closure in ethanol in the presence of catalytic amount of acetic acid provides XII. Removal of the benzyl group using boron tribromide or palladium hydroxide on carbon and cyclohexene yields VII.

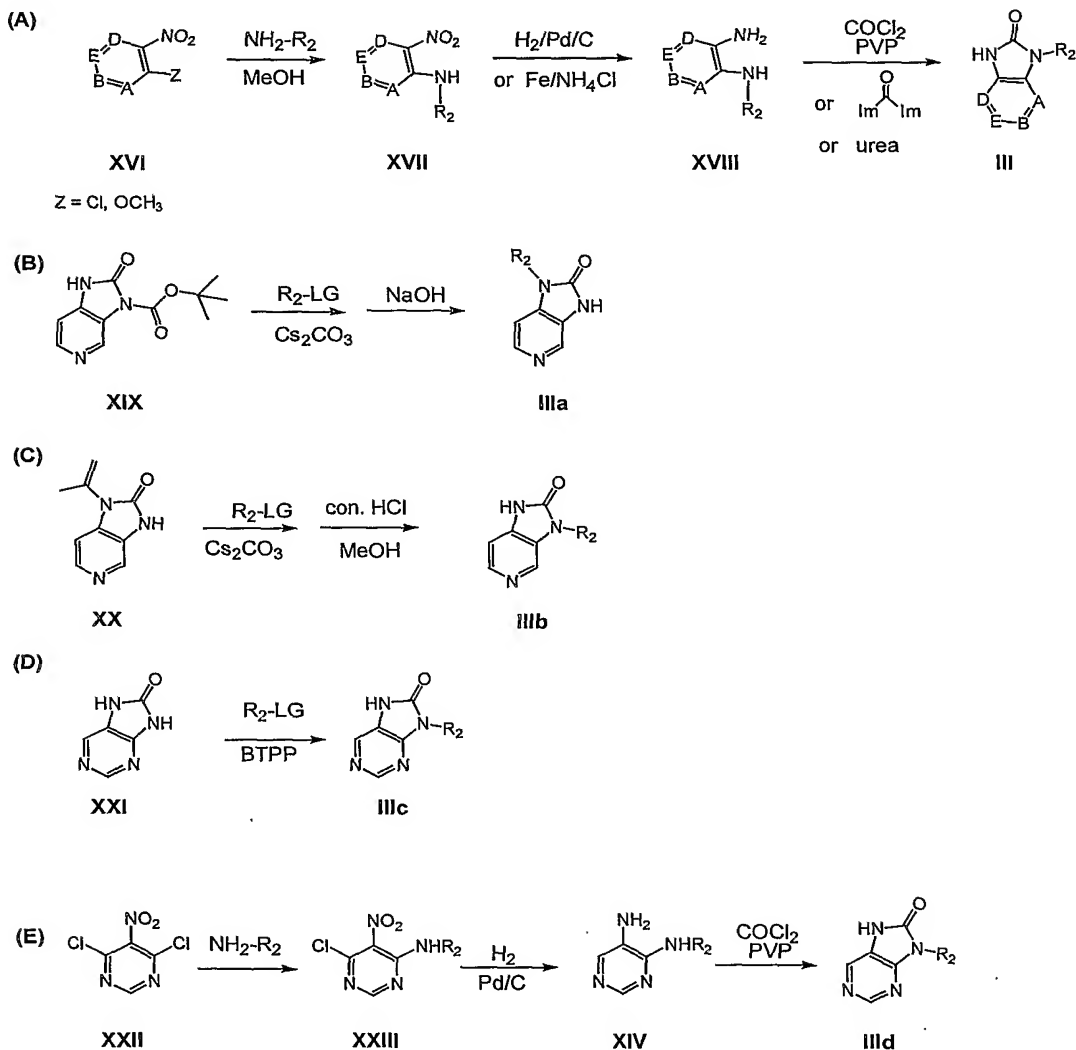
- Preparation of compounds IVa – IVd containing protecting groups is depicted in Schemes II D-F. In Scheme II-D, 2-chloromethylbenzimidazole reacts with methane sulfonyl chloride (Ms-Cl) and triethylamine to give compound IVa. The chloride can be refluxed with potassium iodide in acetone to produce compound IVb. A *p*-methoxybenzyl protecting group is installed in Scheme II-E. Reaction of 4-methoxybenzyl chloride with 2-hydroxymethyl benzimidazole (VI) in the presence of base, preferably sodium hydride, gives compound of Formula XIV. Treatment of alcohol XIV with (bromomethylene)dimethylammonium bromide provides compound IVc. Compound IVd can be prepared as described in Scheme II-F. Michael addition of 2-hydroxymethylbenzimidazole (VI) with acrylonitrile yields compound XV
- 25 which is then converted to the chloride IVd by treatment with thionyl chloride.

Scheme II: Preparation of Benzimidazoles Ia



2-Oxo-imidazopyridines and 2-oxo-imidazopyrimidines can be synthesized using the procedure depicted in Scheme III. Displacement of Z, which is a halide, preferably chlorine, or an alkoxy group, preferably methoxy, of nitropyridines **XVI** (2-chloro-3-nitro-pyridine, 4-alkoxy-3-nitropyridine and 3-alkoxy-2-nitropyridine) with an amine gives **XVII** (Scheme III-A). Reduction of the nitro group and cyclization of the resulting diamine (**XVIII**) using phosgene/polyvinylpyridine, carbonyldiimidazole or urea provides N3-substituted 2-oxo-imidazopyridine **III**. N-substituted 2-oxo-5-imidazo-pyridines **IIIa** are prepared from known compound **XIX** by N-alkylation and deprotection of the *t*-butoxycarbonyl with aqueous sodium hydroxide (Scheme III-B). On the other hand, N-alkylation of **XX** and acid hydrolysis of the isopropenyl group gives 2-oxo-imidazo-6-pyridine **IIIb** (Scheme III-C). 2-Oxo-imidazopyrimidines (**IIIc**) can be prepared directly by reacting 2-oxo-imidazopyrimidine (**XXI**) with R₂-LG where LG is a leaving group as described above, to give **IIIc**, as illustrated in Scheme III-D. Alternatively, 4,6-dichloro-5-nitropyrimidine (**XXII**) is treated with an amine to generate **XXIII** (Scheme III-E). Catalytic reduction of both the nitro group and the carbon-chlorine bond, and cyclization of the resulting diamine (**XIV**) with phosgene provides **IIId**.

Scheme III: Preparation of 2-oxo-imidazopyridines and 2-oxo-imidazopyrimidines



5

Experimental Section

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker Avance 500, AC-300, Bruker DPX-300 or a Varian Gemini 300 spectrometer. All spectra were determined in CDCl₃, CD₃OD, or DMSO-d₆ and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets; dt, doublet of triplets. Mass

spectroscopy was performed on a Finnigan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes or on a LC-MS using Shimadzu LC-10AS with micromass platform LC single quadrupole mass spectrometer in positive electrospray ionization. High resolution mass spectroscopy was recorded using a Finnigan MAT 900. Infrared (IR) spectra were recorded on a Perkin-Elmer system 2000 FT-IR. Elemental analysis was performed with a Perkin-Elmer series II, model 2400 CHN/O/S analyzer. Column chromatography was performed on silica gel from VWR Scientific. Preparative HPLC was performed using a Shimadzu LC-8A on a C18 column eluted with mixture of MeOH in water with 0.1 % trifluoroacetic acid.

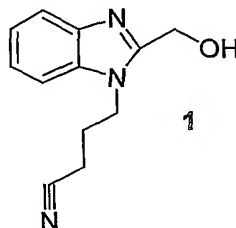
Abbreviations used in the experimental section:

BEMP: 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
BTPP: *t*-butylimino-tri(pyrrolidino)phosphorane
CAN: ceric ammonium nitrate
DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene
DIEA: *N,N*-diisopropylethylamine
DMF: dimethylformamide
DMSO: dimethyl sulfoxide
Et₂O: diethyl ether
EtOAc: ethyl acetate
EtOH: ethyl alcohol
MeOH: methanol
Prep HPLC: preparative high performance liquid chromatography
Prep TLC: preparative thin layer chromatography
TBAF: tetrabutylammonium fluoride
TFA: trifluoroacetic acid
THF: tetrahydrofuran

I. Preparation of Benzimidazoles:

Compounds **1-25**, **59-111**, and **138-143** are benzimidazole intermediates synthesized according to the procedures described in Scheme II.

5



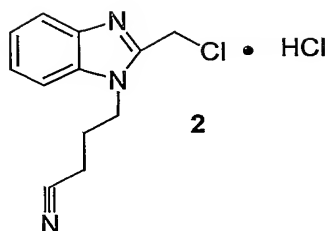
To a solution of 2-hydroxymethylbenzimidazole (29.63 g, 200 mmol) in a mixture of DMF/THF (150 mL, 1:1) was added sodium hydride (60% in mineral oil, 8.4 g, 210 mmol) in several portions at room temperature. After stirring for 1 hour, 4-bromobutyronitrile (29.6 g, 200 mmol) was added and the resulting solution was stirred at 80 °C for 16 hours. The solvent was evaporated and the residue diluted with water and extracted with EtOAc. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:1 to 2:1, then EtOAc/MeOH, 10:1) to give 22.11 g (51% yield) of **1** as a white solid.

¹H NMR (CDCl₃) δ 2.27-2.32 (m, 2 H), 2.41 (t, J = 6.0 Hz, 2 H), 4.41 (t, J = 7.2 Hz, 2 H), 7.26-7.38 (m, 3 H), 7.67-7.70 (m, 1 H);
MS m/e 216 (MH⁺).

General Procedure for Converting 2-Hydroxymethyl-benzimidazoles to 2-Chloromethyl-benzimidazoles.

The procedure described below was used for the synthesis of compounds **2**, **4**, **9**, **11A+11B**, **15**, **19**, **23**, **25**, **70**, **72**, **76**, **81**, **88**, **92**, **94**, **96**, **98**, **100**, **102**, **108**, and **111** and **143**.

20



To alcohol **1** (22 g, 102.2 mmol) suspended in CH_2Cl_2 (100 mL), thionyl chloride (15.81 g, 132.9 mmol) was slowly added with ice-water bath cooling.

- 5 The ice bath was removed. The solution was stirred at room temperature for 1 hour and then evaporated. The residue was triturated with EtOAc to give a nearly quantitative yield of **2** as light gray powder.

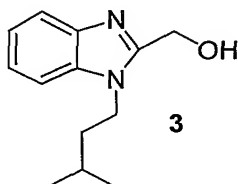
^1H NMR (CDCl_3) δ 2.32-2.38 (m, 2 H), 2.70 (t, $J = 7.3$ Hz, 2 H), 4.69 (t, $J = 7.6$ Hz, 2 H), 5.33 (s, 2 H), 7.69-7.74 (m, 2 H), 7.85-7.87 (m, 1 H), 8.00-8.02 (m, 1 H);

MS m/e 234 (MH^+).

Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_3 \cdot \text{HCl} \cdot 0.25 \text{ H}_2\text{O}$: C, 52.48; H, 4.95; N, 15.30

Found: C, 52.52; H, 4.88; N, 15.26

15



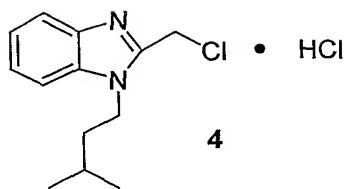
- Compound **3** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 3-methylbutylbromide.

^1H NMR (CDCl_3) δ 1.71-1.78 (m, 3 H), 4.28 (t, $J = 7.5$ Hz, 2 H), 5.02 (s, 2 H), 7.33-7.41 (m, 3 H), 7.75 (d, $J = 7.9$ Hz, 2 H);

MS m/e 219 (MH^+).

25

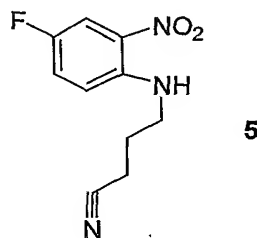
21



Compound **4** was prepared according to the same procedure described for compound **2**.

5

^1H NMR (CDCl_3) δ 1.08 (d, $J = 6.4$ Hz, 6 H), 1.83-1.89 (m, 3 H), 4.57-4.60 (m, 2 H), 5.30 (s, 2 H), 7.68-7.73 (m, 2 H), 7.84-7.86 (m, 1 H), 7.93-7.95 (m, 1 H); MS m/e 237 (MH^+).

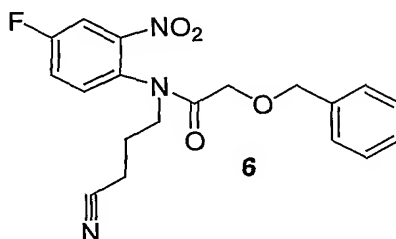


10

A solution of 2,5-difluoronitrobenzene (15.4 g, 96.8 mmol), 4-aminobutyronitrile (7.4 g, 88 mmol) and diisopropylethylamine (23 ml, 132 mmol) in DMF (250 ml) was stirred at room temperature for 32 hours. After filtration, the solvent was evaporated and the orange solid was recrystallized from MeOH (250 ml) to afford **5** (14 g, 65% yield) as orange crystals.

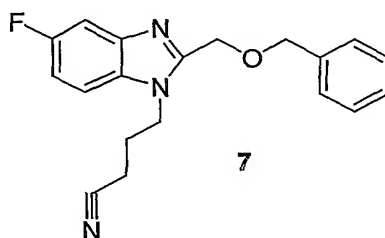
^1H NMR (CDCl_3) δ 2.06-2.12 (m, 2 H), 2.54 (t, $J = 7.0$ Hz, 2 H), 3.48-3.53 (m, 2 H), 6.85-6.88 (m, 1 H), 7.27-7.31 (m, 1 H), 7.89-7.92 (m, 1 H); MS m/e 224 (MH^+).

20



To a suspension of nitrile **5** (10.8 g, 48.4 mmol) and potassium carbonate (20.1 g, 145 mmol) in CH₃CN (200 ml) was added benzyloxyacetyl chloride (7.64 ml, 48.4 mmol) dropwise. After stirring at room temperature for 12 hours, the mixture was diluted with EtOAc (500 ml) and filtered. The filtrate was washed with 1 N HCl, brine, dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 1:1) to yield **6** (7.5 g, 42% yield) as a viscous pale yellow oil.

¹H NMR (CDCl₃) δ 1.86-1.98 (m, 2 H), 2.38-2.51 (m, 2 H), 3.34-3.39 (m, 1 H), 3.80-3.87 (m, 2 H), 4.06-4.14 (m, 1 H), 4.40-4.48 (m, 2 H), 7.18-7.19 (m, 1 H), 7.26-7.40 (m, 5 H), 7.72-7.74 (m, 1 H); MS m/e 394 (MH⁺).



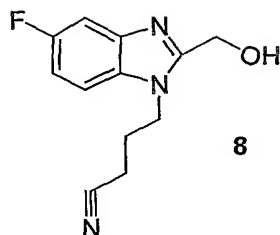
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In a flask equipped with a mechanical stirrer, a suspension of compound **6** (6.40 g, 17.25 mmol), iron powder (2.89 g, 51.8 mmol) and ammonium chloride (4.61 g, 86.2 mmol) in a mixture of MeOH and H₂O (200 ml, 1:1) was stirred at reflux for 4 hours. The mixture was filtered through a pad of Celite and washed with MeOH. The filtrate was evaporated and the residue was taken up in EtOAc (500 ml), washed with brine, dried over MgSO₄, and evaporated. To the residue was added CH₃CN (100 ml) and acetic acid (1 ml), and the mixture was stirred at reflux for 4 hours. The solvent was evaporated and the residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 2:1) to give **7** (4.42 g, 75% yield) as a viscous oil which solidified upon standing.

20
25

¹H NMR (CDCl₃) δ 2.15-2.20 (m, 2 H), 2.31 (t, J = 7.0 Hz, 2 H), 4.35 (t, J = 7.2 Hz, 2 H), 4.62 (s, 2 H), 4.83 (s, 2 H), 7.07-7.11 (m, 1 H), 7.29-7.38 (m, 6 H), 7.43-7.46 (dd, J = 2.4, 9.2 Hz, 1 H);

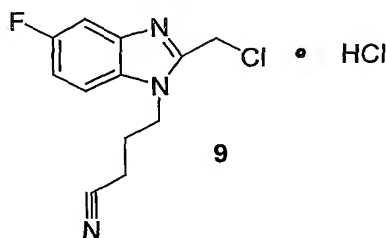
MS m/e 324 (MH⁺).



5 To a solution of **7** (3.23 g, 10 mmol) in CH₂Cl₂ (100 ml) at 0 °C was added boron tribromide (2.84 ml, 30 mmol). After stirring for 1 hour, the mixture was quenched with saturated NaHCO₃ solution with ice bath cooling and extracted with EtOAc. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient,
10 CH₂Cl₂/MeOH, 40:1 to 20:1) to give **8** (1.68 g, 72% yield) as an off-white solid.

¹H NMR (CDCl₃) δ 2.25-2.30 (m, 2 H), 2.43 (t, J = 7.1 Hz, 2 H), 4.41 (t, J = 7.1 Hz, 2 H), 4.85 (s, 2 H), 7.04-7.081 (m, 1 H), 7.29-7.34 (m, 2 H);
MS m/e 234 (MH⁺).

15



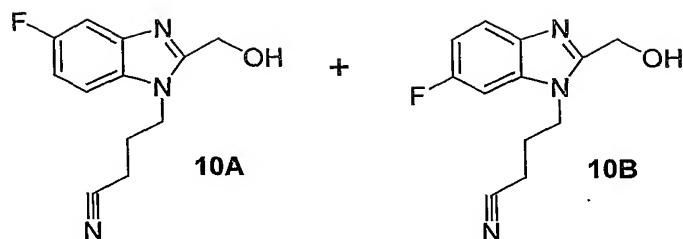
Compound **9** was prepared according to the same procedure described for compound **2**.

20

¹H NMR (CD₃OD) δ 2.30-2.36 (m, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 4.67 (t, J = 7.6 Hz, 2 H), 5.30 (s, 2 H), 7.49-7.54 (dt, J = 2.4, 9.2 Hz, 1 H), 7.62-7.64 (dd, J = 2.4, 8.0 Hz, 1 H), 8.01-8.04 (dd, J = 2.0, 9.2 Hz, 1 H);
MS m/e 252 (MH⁺).

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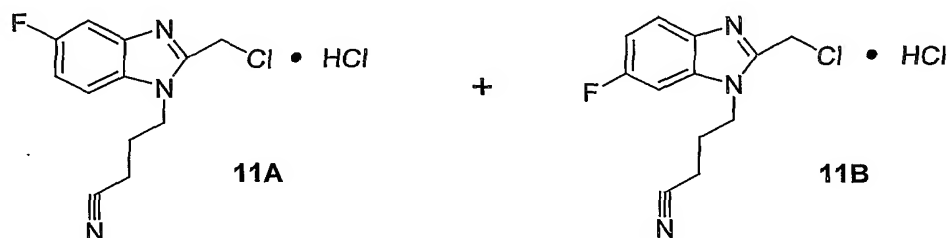
24



A mixture of **10A** and **10B** was prepared from 5-fluoro-2-hydroxymethylbenzimidazole using the same procedure described for compound **1**.

5

^1H NMR (CDCl_3) δ 2.26-2.30 (m, 2 H), 2.42-2.46 (m, 2 H), 4.36-4.42 (m, 2 H), 4.87 (s, 2 H), 7.03-7.07 (m, 1.5 H), 7.30-7.32 (m, 1 H), 7.60-7.63 (m, 0.5 H); MS m/e 234 (MH^+).

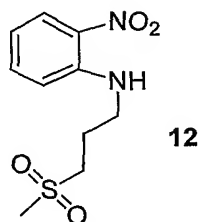


10

Compounds **11A** and **11B** were prepared according to the same procedure described for compound **2**.

15 ^1H NMR (CDCl_3) δ 2.24-2.30 (m, 2 H), 2.44-2.47 (m, 2 H), 4.32-4.39 (m, 2 H), 4.829 (s, 1 H), 4.831 (s, 1 H), 7.01-7.11 (m, 1.5 H), 7.30-7.33 (dd, $J = 4.4, 8.8$ Hz, 0.5 H), 7.40-7.42 (dd, $J = 2.3, 9.0$ Hz, 0.5 H), 7.66-7.68 (dd, $J = 4.8, 8.8$ Hz, 0.5 H); MS m/e 252 (MH^+).

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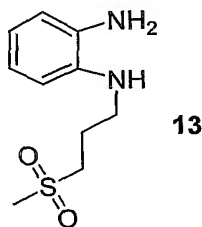
2-Fluoronitrobenzene (35.4 g, 250.9 mmol), 3-(methylthio)propylamine (24.0g, 228.1 mmol) and potassium carbonate (47.3 g, 342 mmol) were stirred in CH₃CN (100 mL) at room temperature overnight. After stirring for an additional hour at reflux, the mixture was cooled to room temperature and filtered. The
5 filtrate was evaporated. To the residue in DMF (150 mL), magnesium monoperoxyphthalate hexahydrate (MMPP, 168 g, 340 mmol) was added in several portions with ice-water cooling. The mixture was stirred at room temperature for 3 hours and the solvent was evaporated. The residue was dissolved in CH₂Cl₂ and washed with 1 N NaOH, water, brine, dried over MgSO₄
10 and evaporated. The residue was triturated with hot EtOAc to give **12** (48.7 g, 75% yield) as an orange solid.

¹H NMR (CDCl₃) δ 2.25-2.35 (m, 2 H), 2.97 (s, 3 H), 3.17 (t, J = 7.2 Hz, 2 H), 3.59 (t, J = 6.9 Hz, 2 H), 6.68 -6.74 (m, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 7.45-7.51
15 (m, 1 H), 8.20 (dd, J = 1.5, 8.7 Hz, 1 H);

MS m/e 259 (MH⁺);

Anal. Calcd for C₁₀H₁₄N₂O₄S: C, 46.50; H, 5.46; N, 10.84

Found: C, 46.53; H, 5.54; N, 10.90.

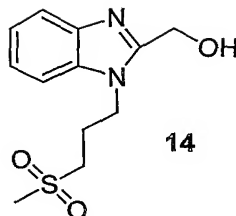


20

To a suspension of **12** (48.5 g, 187.8 mmol) in a mixture of CHCl₃ and MeOH (150 mL, 1:3) was added 10% palladium on carbon (6 g) under nitrogen. The reduction was carried out in a Parr shaker with hydrogen pressure maintained
25 between 40 and 60 psi for 25 minutes. The catalyst was removed by filtration through a pad of Celite and the filtrate was evaporated to give crude **13**.

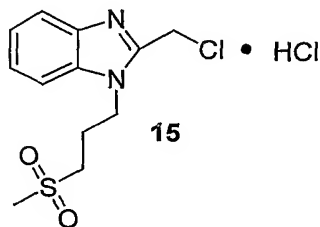
¹H NMR (CD₃OD) δ 2.11-2.21 (m, 2 H), 2.98 (s, 3 H), 3.28-3.36 (m, 4 H), 6.75 (dt, J = 0.9, 7.2 Hz, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 7.06-7.12 (m, 2 H);

MS m/e 229 (MH^+).



5 The crude diamine **13** obtained above was stirred at reflux overnight with glycolic acid (15.7 g, 207 mmol) in 6 N HCl (150 mL). The solution was cooled in an ice bath and neutralized with concentrated NH_4OH solution, extracted with EtOAc, dried over MgSO_4 and evaporated. The residue was purified by chromatography (gradient, EtOAc/hexane, 1:1 to EtOAc/MeOH, 10:1) to give a product which crystallized from EtOAc/MeOH to afford 25.7 g (51% yield in two steps) of **14**.

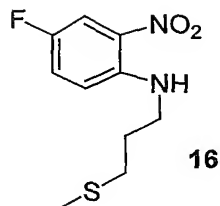
^1H NMR (CD_3OD) δ 2.38-2.44 (m, 2 H), 2.97 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H), 4.54 (t, $J = 7.6$ Hz, 2 H), 7.27 (t, $J = 1.1, 8.1$ Hz, 1 H), 7.33 (dt, $J = 1.1, 8.0$ Hz, 1 H), 7.62 (d, $J = 8.1$ Hz, 1 H), 7.64 (dd, $J = 1.0, 8.0$ Hz, 1 H);
15 MS m/e 269 (MH^+).



20 Compound **15** was prepared according to the same procedure described for compound **2**.

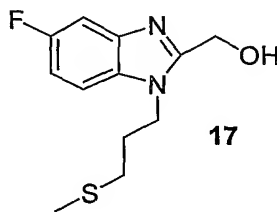
^1H NMR (CD_3OD) δ 2.46-2.52 (m, 2 H), 3.03 (s, 3 H), 3.37 (t, $J = 7.1$ Hz, 2 H), 4.77 (t, $J = 7.8$ Hz, 2 H), 5.31 (s, 2 H), 7.68-7.73 (m, 2 H), 7.86 (dd, $J = 2.8, 6.9$ Hz, 1 H), 8.03 (dd, $J = 1.7, 6.1$ Hz, 1 H);
25

MS m/e 287 (MH^+).



To a solution of 2,5-difluoronitrobenzene (15.1 g, 95.06 mmol) in CH_3CN (150 mL) was added potassium carbonate (26.3 g, 190.11 mmol) and 3-(methylthio)propylamine (10.0 g, 95.06 mmol). The mixture was stirred vigorously with the aid of a mechanical stirrer for 16 hours at room temperature. The solid was filtered and the filtrate was evaporated. The residue was diluted with EtOAc (600 mL) and washed with water and brine. The organic layer was dried over anhydrous MgSO_4 and evaporated to give crude **16** as an orange solid (25 g, 70% pure).

^1H NMR (CDCl_3) δ 1.97-2.01 (m, 2 H), 2.11 (s, 3 H), 2.62 (t, $J = 6.9$ Hz, 2 H), 3.43 (q, $J = 6.3$ Hz, 2 H), 6.87 (dd, $J = 4.6, 9.3$ Hz, 1 H), 7.22-7.24 (m, 1 H), 7.85 (dd, $J = 3.1, 9.3$ Hz, 1 H), 7.95 (bs, 1 H); MS m/e 245 (MH^+).



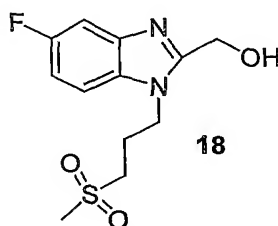
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A solution of **16** (25 g) in MeOH (300 mL) was added to a mixture of iron powder (12.0 g, 214.9 mmol) and ammonium chloride (19.2 g, 358.2 mmol) in water (100 mL). The reaction mixture was vigorously stirred with a mechanical stirrer and heated at 90 °C for 16 hours. The mixture was filtered through a plug of Celite which was rinsed with hot methanol. The solvent was evaporated to give the crude diamine. LC-MS m/e 215 (MH^+).

25

The diamine (500 mg crude, 2.33 mmol) and glycolic acid (266 mg, 3.50 mmol) were heated at reflux in 4 N hydrochloric acid (15 mL) for 16 hours. The aqueous solution was cooled and neutralized with concentrated NH_4OH (15 mL). The aqueous solution was then extracted with EtOAc. The organic extracts were dried over anhydrous MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexanes, 2:1 to EtOAc/MeOH, 10:1) to give **17** (150 mg, 25% yield).

^1H NMR (CD_3OD) δ 2.08 (s, 3 H), 2.12-2.20 (m, 2 H), 2.53 (t, $J = 6.9$ Hz, 2 H), 4.43 (t, $J = 6.3$ Hz, 2 H), 4.85 (s, 2 H), 7.07 (dt, $J = 2.4, 9.2$ Hz, 1 H), 7.30 (dd, $J = 2.4, 9.3$ Hz, 1 H), 7.53 (dd, $J = 4.6, 8.9$ Hz, 1 H); MS m/e 255 (MH^+).



15

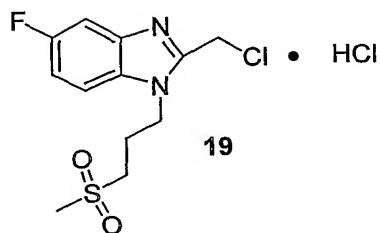
To a solution of sulfide **17** (150 mg, 0.59 mmol) in DMF (5 mL) was added magnesium monoperoxyphosphate hexahydrate (MMPP, 583 mg, 1.18 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated, and the residue was diluted with water and extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) to give **18** (129 mg, 76% yield) as a white solid.

^1H NMR (CD_3OD) δ 2.37-2.47 (m, 2 H), 3.00 (s, 3 H), 3.26 (t, $J = 7.4$ Hz, 2 H), 4.55 (t, $J = 7.5$ Hz, 2 H), 7.14 (dt, $J = 2.4, 9.4$ Hz, 1 H), 7.34 (dd, $J = 2.4, 9.2$ Hz, 1 H), 7.62 (dd, $J = 4.5, 8.9$ Hz, 1 H); IR (KBr, cm^{-1}) 3139, 1624, 1591, 1489, 1478, 1446, 1416, 1308, 1270, 1143, 1134, 1047, 951, 859, 802, 527, 500;

MS m/e 287 (MH^+);

Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{FN}_2\text{O}_3\text{S}$: C, 50.33; H, 5.28; N, 9.78

Found: C, 50.17; H, 5.17; N, 9.57.

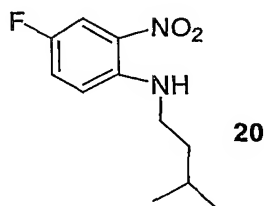


5

Compound **19** was prepared according to the same procedure described for compound **2**.

- 10 ^1H NMR ($\text{DMSO}-d_6$) δ 2.15-2.20 (m, 2 H), 3.00 (s, 3 H), 3.26 (t, $J = 7.2$ Hz, 2 H), 4.47 (t, $J = 7.8$ Hz, 2 H), 5.11 (s, 2 H), 7.27 (dt, $J = 2.4, 9.4$ Hz, 1 H), 7.51 (dd, $J = 2.4, 9.0$ Hz, 1 H), 7.76 (dd, $J = 4.8, 9.0$ Hz, 1 H);
IR (KBr, cm^{-1}) 3429, 2577, 1635, 1536, 1496, 1290, 1277, 1130, 962, 927, 784;
MS m/e 305 (MH^+).

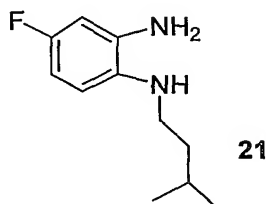
15



- To a solution of 2,5-difluoronitrobenzene (45 g, 282.86 mmol) in CH_3CN (500 mL) was added potassium carbonate (78 g, 565.72 mmol) and isoamylamine (25 g, 282.86 mmol). The reaction mixture was stirred at room temperature for 18 hours with the aid of a mechanical stirrer. The potassium carbonate was filtered and the filtrate was evaporated to give an orange oil. The oil was diluted with EtOAc, washed with water and brine, dried over MgSO_4 , and evaporated. Purification by flash column chromatography (hexanes/EtOAc, 20:1) gave 53 g (83% yield) of compound **20**.

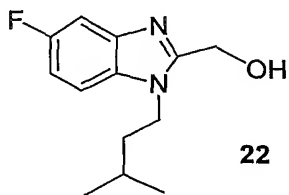
25

^1H NMR (CDCl_3) δ 0.98 (d, $J = 6.5$ Hz, 6 H), 1.61-1.65 (m, 2 H), 1.74-1.78 (m, 1 H), 3.30 (t, $J = 7.3$ Hz, 2 H), 6.83 (dd, $J = 4.6, 9.5$ Hz, 1 H), 7.23-7.27 (m, 1 H), 7.85 (dd, $J = 3.1, 9.2$ Hz, 1 H).



To a solution of compound **20** (53 g, 235.14 mmol) and concentrated HCl (15 mL) in MeOH (200 mL) was added 10% palladium on carbon (5 g) and the mixture was agitated under H_2 at 55 psi for 1.5 hours. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give 47 g (87% yield) of diamine **21** as the HCl salt.

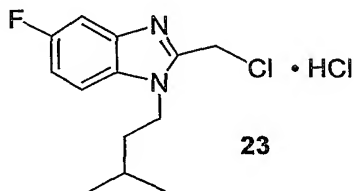
^1H NMR (CDCl_3) δ 0.97 (d, $J = 6.2$ Hz, 6 H), 1.65-1.77 (m, 3 H), 3.36 (t, $J = 8.0$ Hz, 2 H), 6.50-6.57 (m, 1 H), 6.71 (dd, $J = 2.7, 10.5$ Hz, 1 H), 7.28 (dd, $J = 5.5, 8.8$ Hz, 1 H); MS m/e 197 (MH^+).



A mixture of diamine **21** (47 g, 200.66 mmol) and glycolic acid (16 g, 210.70 mmol) in 4 N HCl (500 mL) was stirred at reflux for 18 hours. The reaction mixture was cooled first to room temperature and then to 0 °C. The reaction was diluted with concentrated ammonium hydroxide (200 mL) until the pH was adjusted to approximately 8. The product was extracted with EtOAc, dried over MgSO_4 , and evaporated. The crude product was recrystallized with EtOAc/hexanes to give 27 g (37% yield) of compound **22** as brown crystals.

^1H NMR (CDCl_3) δ 1.02 (d, $J = 6.0$ Hz, 6 H), 1.68-1.75 (m, 3 H), 3.19 (bs, 1 H), 4.22 (t, $J = 7.7$ Hz, 2 H), 4.93 (s, 2 H), 7.06 (dt, $J = 2.2, 9.1$ Hz, 1 H), 7.26-7.28 (m, 1 H), 7.37 (dd, $J = 2.1, 8.9$ Hz, 1 H);
MS m/e 237 (MH^+).

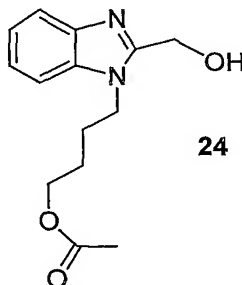
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Compound **23** was prepared according to the same procedure described for compound **2**.

10

^1H NMR (CDCl_3) δ 1.08 (d, $J = 6.4$ Hz, 6 H), 1.79-1.90 (m, 3 H), 4.44 (bt, $J = 8.2$ Hz, 2 H), 5.32 (s, 2 H), 7.36 (dt, $J = 2.2, 8.9$, 1 H), 7.54-7.59 (m, 2 H);
MS m/e 255 (MH^+).



15

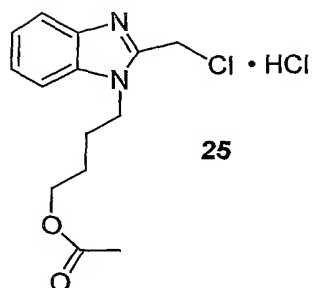
Compound **24** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 4-bromobutyl acetate.

20

^1H NMR (CDCl_3) δ 1.68-1.72 (m, 2 H), 1.91-1.94 (m, 2 H), 2.03 (s, 3 H), 4.07 (t, $J = 6.4$ Hz, 2 H), 4.26 (t, $J = 7.5$ Hz, 2 H), 4.86 (s, 2 H), 6.86 (bs, 1 H), 7.20-7.29 (m, 3 H), 7.65 (dd, $J = 1.8, 6.7$ Hz, 1 H);
MS m/e 263 (MH^+).

25

32

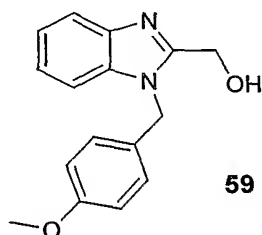


Compound **25** was prepared according to the same procedure described for compound **2**.

5

^1H NMR (CDCl_3) δ 1.80-1.86 (m, 2 H), 2.03 (s, 3 H), 2.06-2.12 (m, 2 H), 4.14 (t, $J = 6.1$ Hz, 2 H), 4.55 (t, $J = 8.1$ Hz, 2 H), 5.42 (s, 2 H), 7.48 (t, $J = 7.3$ Hz, 1 H), 7.55 (t, $J = 7.3$ Hz, 1 H), 7.64 (d, $J = 8.5$ Hz, 1 H), 7.78 (d, $J = 8.2$ Hz, 1 H); MS m/e 281 (MH^+).

10

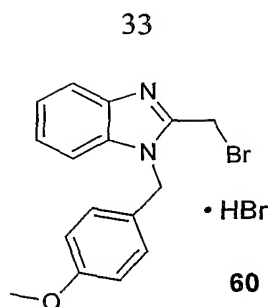


Compound **59** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 4-methoxybenzyl chloride.

15

^1H NMR (CDCl_3) δ 3.77 (s, 3 H), 4.99 (s, 2 H), 5.45 (s, 2 H), 6.84 (d, $J = 8.6$ Hz, 2 H), 7.11 (d, $J = 8.6$ Hz, 2 H), 7.28-7.34 (m, 3 H), 7.75 (d, $J = 6.8$, 1 H); MS m/e 269 (MH^+).

20



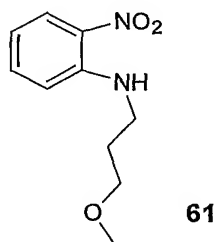
Compound **59** (4.75 g, 17.7 mmol) was combined with CH_2Cl_2 (100 mL) and the mixture was treated with (bromomethylene)dimethylammonium bromide (5.25 g, 23.0 mmol). The reaction was stirred at room temperature for 30 minutes and then filtered to isolate a white solid. The solid was rinsed with CH_2Cl_2 , then with diethyl ether. The solid was triturated with water (50 mL), isolated by filtration, rinsed with water, then with acetone, and finally with Et_2O . The white powder was labeled crop 1 and set aside. All liquids were combined and concentrated in vacuo to give an off-white solid which was triturated with a mixture of acetone (50 mL) and Et_2O (300 mL). The liquid was decanted and the solid was suspended in acetone and isolated by filtration to give crop 2. Crops 1 and 2 were determined to be spectroscopically identical and were combined to give 6.65 g (91 % yield) of compound **60** as a white powder.

15

^1H NMR ($\text{DMSO}-d_6$) δ 3.72 (s, 3 H), 5.18 (s, 2 H), 5.68 (s, 2 H), 6.92 (d, $J = 8.7$ Hz, 2 H), 7.29 (d, $J = 8.7$ Hz, 2 H), 7.44-7.47 (m, 2 H), 7.62-7.63 (m, 1 H), 7.78-7.80 (m, 1 H);

MS m/e 332 (MH^+).

20

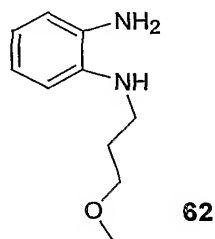


Compound **61** was prepared according to the same procedure described for compound **16** using 3-methoxypropylamine instead of 3-(methylthio)propylamine.

25

^1H NMR (CDCl_3) δ 1.95-2.00 (m, 2 H), 3.37 (s, 3 H), 3.39-3.43 (m, 2 H), 3.52 (t, $J = 5.7$ Hz, 2 H), 6.61 (t, $J = 8.2$ Hz, 1 H), 6.86 (d, $J = 8.8$ Hz, 1 H), 7.41 (t, $J = 7.9$ Hz, 1 H), 8.14 (dd, $J = 1.4, 8.7$ Hz, 1 H), 8.26 (bs, 1 H);
MS m/e 211 (MH^+).

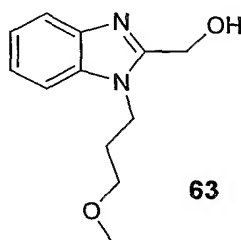
5



Compound **62** was prepared from compound **61** according to the same procedure described for compound **13** and was used immediately upon isolation.

10

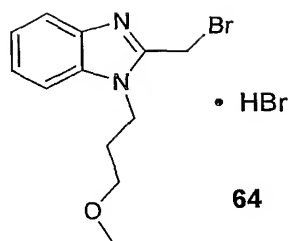
MS m/e 181 (MH^+).



15 Compound **63** was prepared from compound **62** according to the same procedure described for compound **14**.

^1H NMR (CDCl_3) δ 2.09-2.14 (m, 2 H), 3.30 (t, $J = 5.7$ Hz, 2 H), 3.33 (s, 3 H), 4.35 (t, $J = 6.9$ Hz, 2 H), 4.89 (s, 2 H), 7.22-7.26 (m, 2 H), 7.35-7.37 (m, 1 H),
20 7.69-7.70 (m, 1 H);
MS m/e 221 (MH^+).

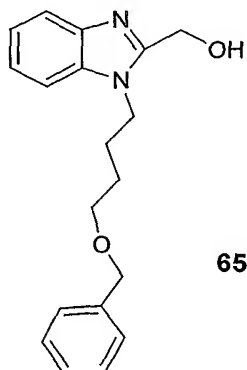
35



A solution of compound **63** (1.50 g, 6.81mmol) in CH₃CN (20 mL) was treated with (bromomethylene)dimethylammonium bromide. The reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with H₂O (3 mL) and the solvent was evaporated and dried under vacuum to give compound **64** which was used immediately upon isolation.

MS m/e 283, 285 (MH⁺).

10



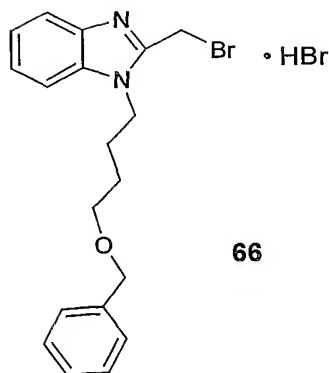
Compound **65** was prepared according to the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with benzyl 4-bromobutylether.

15

¹H NMR (CD₃OD) δ 1.65-1.71 (m, 2 H), 1.94-1.99 (m, 2 H), 3.52 (t, J = 6.2 Hz, 2 H), 4.36 (t, J = 7.7 Hz, 2 H), 4.47 (s, 2 H), 4.84 (s, 2 H), 7.22-7.27 (m, 3 H), 7.27-7.31 (m, 4 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.61 (dd, J = 1.4, 7.1 Hz, 1 H);

20 MS m/e 311 (MH⁺).

36

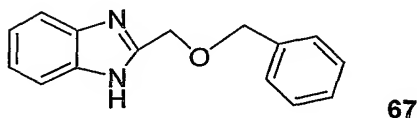


66

Compound 66 was prepared according to the same procedure described for compound 64.

5

MS m/e 373, 375 (MH⁺).

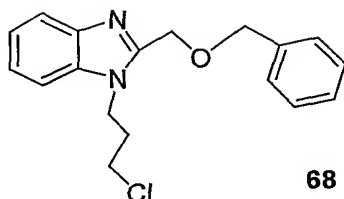


67

10 To a suspension of 1,2-phenylenediamine (50 g, 462 mmol) in THF (150 mL) cooled at 0°C was slowly added a solution of benzyloxyacetyl chloride (171 g, 924 mmol) in THF (100 mL). The reaction mixture was stirred for 3 hours. The reaction mixture was cooled to 0 °C with an ice bath and 4N HCl (300 mL) was slowly added to the reaction mixture. The ice bath was removed and the mixture was heated at reflux for 18 hours. The majority of the THF was evaporated. The aqueous material was neutralized with 10 N NaOH, extracted with EtOAc, dried over MgSO₄, and evaporated to give a tan solid. The solid was recrystallized from EtOAc to give 45 g (41% yield) of compound 67.

20 ¹H NMR (CD₃OD) δ 4.65 (s, 2 H), 4.77 (s, 2 H), 7.22-7.41 (m, 7 H), 7.56 (dd, J = 3.2, 6.1 Hz, 2 H);
MS m/e 239 (MH⁺).

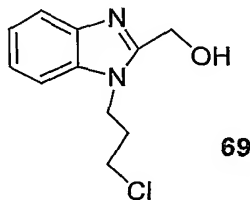
37



68

To a solution of compound **67** (6.00 g, 25.18 mmol) in DMF (50 mL) was added sodium hydride (60% dispersion in mineral oil, 1.46 g, 36.52 mmol). The reaction mixture was cooled to 0 °C and stirred for 30 minutes. To the cooled mixture 1-bromo-3-chloropropane (5.35 g, 32.99 mmol) was added and the reaction mixture was stirred for 4.5 hours. The mixture was diluted with H₂O (75 mL) and extracted with Et₂O (3 x 300 mL). The combined organic extracts were dried over MgSO₄ and evaporated. Purification by flash column chromatography on silica (gradient, hexanes/EtOAc 2:1 to 1:1) gave 6.86 g (87% yield) of compound **68**.

¹H NMR (CDCl₃) δ 2.22-2.36 (m, 2 H), 3.53 (t, J = 6.0 Hz, 2 H), 4.45 (t, J = 7.0 Hz, 2 H), 4.62 (s, 2 H), 4.90 (s, 2 H), 7.28-7.44 (m, 7 H), 7.42-7.48 (m, 1 H), 7.79-7.82 (m, 1 H); MS m/e 315, 317 (MH⁺).



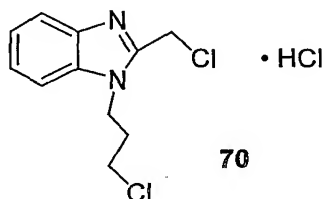
69

A solution of compound **68** (4.00 g, 12.71 mmol) in CH₂Cl₂ (75 mL) was cooled to 0 °C with an ice bath. To this solution was added boron tribromide (0.99M in CH₂Cl₂, 20 mL, 19.76 mmol) slowly via syringe. The reaction mixture was stirred at 0 °C for 2 hours. The reaction was quenched at 0 °C with MeOH (75 mL). The solvent was evaporated with a room temperature rotary evaporator bath. More MeOH was added and was again evaporated. The resulting solid was dried under high vacuum for 48 hours to give 3.70 g (95% yield) of compound **69**.

^1H NMR (CD_3OD) δ 2.39-2.44 (m, 2 H), 3.72 (t, $J = 6.0$ Hz, 2 H), 4.61 (t, $J = 7.2$ Hz, 2 H), 5.19 (s, 2 H), 7.62-7.68 (m, 2 H), 7.80-7.82 (m, 1 H), 7.93-7.95 (m, 1 H);

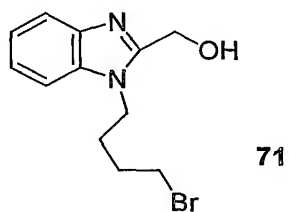
MS m/e 225, 227 (MH^+).

5



Compound 70 was prepared according to the same procedure described for compound 2.

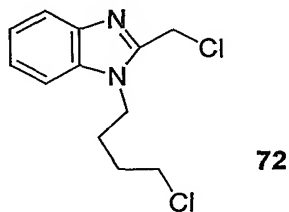
10 MS m/e 244 (MH^+).



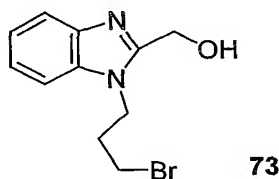
Compound 71 was prepared according to the same procedure described for compound 1 using 1,4-dibromobutane and the reaction was carried out at 0 °C.

^1H NMR (CD_3OD) δ 1.91-1.95 (m, 2 H), 2.01-2.08 (m, 2 H), 3.48 (t, $J=6.6$ Hz, 2 H), 4.38 (t, $J=7.4$ Hz, 2 H), 4.86 (s, 2 H), 7.23-7.27 (m, 1 H), 7.29-7.32 (m, 1H), 7.54 (d, $J=8.0$ Hz, 1 H), 7.62 (d, $J=8.0$ Hz, 1 H);

20 MS m/e 282, 284 (MH^+).



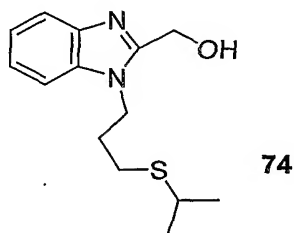
Compound **72** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.



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Compound **73** was prepared according to the same procedure described for compound **1** using 1,3 dibromopropane and the reaction was carried out at 0 °C.

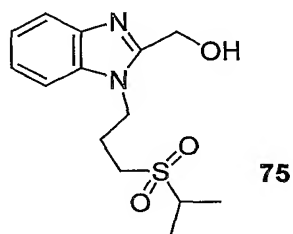
¹H NMR (CDCl₃) δ 2.42-2.47 (m, 2 H), 3.43 (t, J= 6.1 Hz, 2 H), 4.43 (t, J=7.0 Hz, 2 H), 4.94 (s, 2 H), 7.25-7.32 (m, 2 H), 7.42-7.44 (m, 1 H), 7.68-7.70 (m, 1 H);
10 MS m/e 268, 270 (MH⁺).



15 2-Propanethiol (305 mg, 4.00 mmol) and sodium hydride (60% dispersion in mineral oil, 240 mg, 6.00 mmol) were stirred together in DMF (20 mL) and then cooled to 0 °C. To this mixture was added compound **73** (542 mg, 2.00 mmol) and the reaction mixture was allowed to warm to room temperature over 2 hours. The reaction mixture was quenched with water and extracted with EtOAc.
20 The combined organic extracts were washed with water and brine, dried over MgSO₄, and evaporated. Purification by column chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) gave 310 mg (59% yield) of compound **74** as an off-white oil.

^1H NMR (CD_3OD) δ 1.22 (d, $J = 6.7$ Hz, 6 H), 2.10-2.18 (m, 2 H), 2.58 (t, $J=7.0$ Hz, 2 H), 2.90-2.93 (m, 1 H), 4.45 (t, $J=7.3$ Hz, 2 H), 4.87 (s, 2 H), 7.23-7.32 (m, 2 H), 7.55 (d, $J=8.0$ Hz, 1 H), 7.62 (d, $J=7.9$ Hz, 1 H);

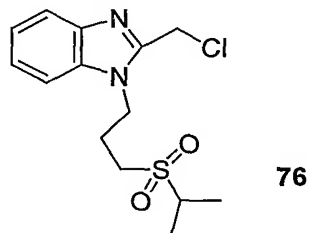
5 MS m/e 265 (MH^+).



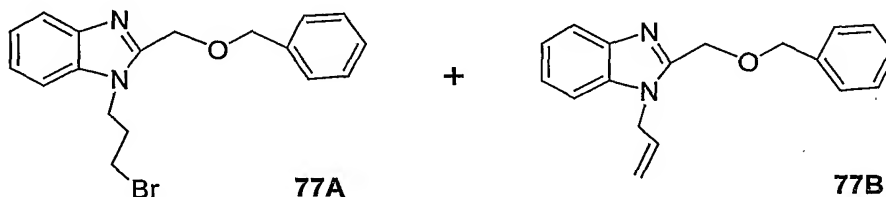
10 Compound 75 was prepared from compound 74 according to the same procedure described for compound 18.

^1H NMR (CD_3Cl) δ 1.32-1.36 (m, 6 H), 2.44-2.50 (m, 2 H), 3.00-3.02 (m, 2 H), 3.06-3.10 (m, 1 H), 4.48 (t, $J=7.3$ Hz, 2 H), 4.87 (s, 2 H), 7.23-7.30 (m, 2 H), 7.42 (d, $J=7.7$ Hz, 1 H), 7.65 (d, $J=7.8$ Hz, 1 H);

15 MS m/e 297 (MH^+).



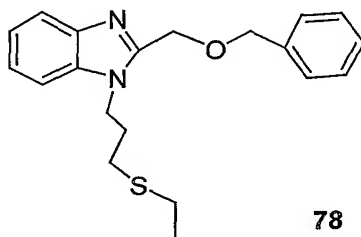
20 Compound 76 was prepared according to the same procedure described for compound 2 and was used immediately upon isolation.



To a solution of compound **67** (18.25 g, 76.59 mmol) in DMF (85 mL) was added sodium hydride (60% dispersion in mineral oil, 3.37 g, 84.25 mmol). The reaction mixture was stirred for 30 minutes and then cooled to 0 °C. 1,3-Dibromopropane was slowly added to the cooled solution. The temperature was raised to room temperature after 20 minutes as no starting material remained. The reaction mixture was diluted with H₂O and extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and evaporated. Column chromatography (hexanes/EtOAc, 2:1) gave 5.2 g of a 60/40 mixture of the desired bromide compound **77A** (8% yield) and an undesired elimination product **77B**. This mixture was used in the next step without further purification.

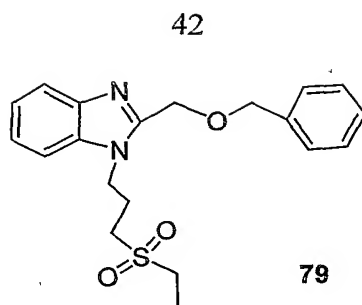
Bromide **77A** : MS m/e 360,361 (MH⁺);

Elimination product **77B** : MS m/e 279 (MH⁺).



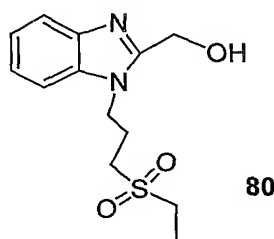
15

To a solution of ethanethiol (1.04 g, 16.77 mmol) in DMF (60 mL) was added sodium hydride (60% dispersion in mineral oil, 670 mg, 16.77 mmol). The mixture was stirred for 15 minutes at room temperature and then cooled to 0 °C. In a separate flask, the mixture containing compounds **77A** and **77B** (5.2 g mixture, 3.0 g, 8.38 mmol) was dissolved in DMF (10 mL), cooled to 0 °C and added slowly to the ethanethiol mixture. The reaction mixture was stirred for 1 hour while the temperature was slowly allowed to rise to room temperature. The DMF was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with H₂O. The organic layer was dried over MgSO₄ and evaporated. This material containing compound **78** was used immediately as a mixture without further purification.



Compound **79** was prepared from crude **78** according to the same procedure as compound **18** and was purified by flash column chromatography on silica (gradient, EtOAc/hexanes, 2:1 to straight EtOAc).

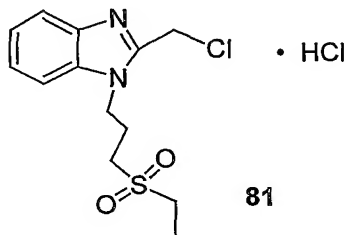
^1H NMR (CDCl_3) δ 1.21 (t, $J = 7.5$ Hz, 3 H), 2.35-2.42 (m, 2 H), 2.73 (q, $J = 7.5$ Hz, 2 H), 2.84-2.88 (m, 2 H), 4.43 (t, $J = 7.2$ Hz, 2 H), 4.60 (s, 2 H), 4.87 (s, 2 H), 7.27-7.34 (m, 5 H), 7.42 (dd, $J = 1.5, 7.0$ Hz, 1 H), 7.77 (dd, $J = 1.6, 6.9$ Hz, 1 H), 8.00 (s, 2 H);
MS m/e 373 (MH^+).



A solution of compound **79** (1.95 g, 5.24 mmol) in CH_2Cl_2 (50 mL) was cooled to 0°C with an ice bath. To this solution was added boron tribromide (0.99 M in CH_2Cl_2 , 9.0 mL, 9.00 mmol) slowly via syringe. The reaction mixture was stirred for 40 minutes at 0°C before quenching at 0°C by cautious addition of anhydrous MeOH (50 mL). The solvent was evaporated with a room temperature rotary evaporator bath. More anhydrous MeOH was added and the solvent was again evaporated. The resulting solid was dried under high vacuum for 48 hours to give 1.82 g (96% yield) of compound **80**.

^1H NMR (DMSO- d_6) δ 1.22 (t, J = 7.4 Hz, 3 H), 2.23-2.89 (m, 2 H), 3.11 (q, J = 7.4 Hz, 2 H), 3.29 (t, J = 7.7 Hz, 2 H), 4.53 (t, J = 7.5 Hz, 2 H), 5.08 (s, 2 H), 7.58-7.65 (m, 2 H), 7.80 (dd, J = 1.0, 7.3 Hz, 1 H), 8.04 (d, J = 7.75 Hz, 1 H); MS m/e 283 (MH^+).

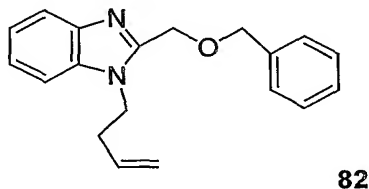
5



Compound **81** was prepared according to the same procedure described for compound **2**.

10

MS m/e 301 (MH^+).

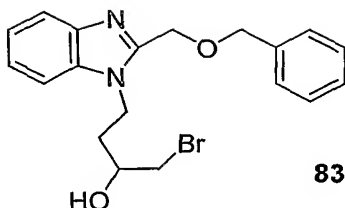


15 To a solution of compound **67** (1.43 g, 6.00 mmol) in DMF (25 mL) was added sodium hydride (60% dispersion in mineral oil, 260 mg, 6.60 mmol) and the mixture was cooled to 0 °C. To the mixture was added 4-bromo-1-butene (972 mg, 7.20 mmol) and the mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was quenched with H_2O and extracted with
20 EtOAc. The organic extracts were washed with water and then brine, dried over MgSO_4 , and evaporated. Flash column chromatography (gradient, hexanes /EtOAc, 4:1 to 1:1) gave 580 mg (33% yield) of compound **82** as a viscous oil.

^1H NMR (CDCl_3) δ 2.55-2.59 (m, 2 H), 4.31 (t, J =7.5 Hz, 2 H), 4.59 (s, 2 H), 4.88 (s, 2 H), 5.01 (d, J =7.8 Hz, 1 H), 5.04 (d, J =10.4 Hz, 1 H), 5.71-5.80 (m, 1 H), 7.26-7.39 (m, 8 H), 7.79 (d, J =7.6 Hz, 1 H);

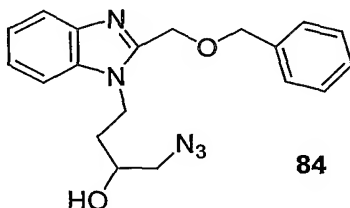
25

MS m/e 293 (MH^+).



5 To a solution of compound **82** (468 mg, 1.92 mmol) and water (71 mg, 3.93 mmol) in DMSO (5 mL) was added N-bromosuccinimide (NBS, 700 mg, 3.93 mmol) at room temperature and the mixture was stirred for 1 hour. The resulting solution was diluted with EtOAc and washed with H₂O. The organic extracts were dried with MgSO₄ and evaporated. The residue was purified by
10 flash chromatography (gradient, hexane:EtOAc 3:1 to 1:2) to give 214 mg (56% yield) of compound **83** as a off-white viscous oil.

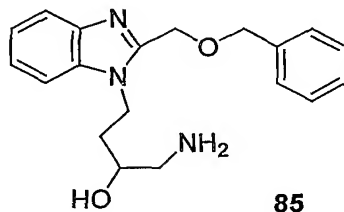
¹H NMR (CDCl₃) δ 1.90-1.97 (m, 1 H), 2.12-2.18 (m, 1 H), 3.22-3.30 (m, 2 H), 3.61-3.66 (m, 1 H), 4.38-4.50 (m, 2 H), 4.59-4.64 (m, 2 H), 4.87-4.92 (m, 2 H),
15 7.28-7.37 (m, 7 H), 7.42-7.46 (m, 1 H), 7.78-7.80 (m, 1 H);
MS m/e 389, 391 (MH^+).



20 A mixture of compound **83** (214 mg, 0.55 mmol) and sodium azide (107 mg, 1.65 mmol) in DMF (5 mL) was stirred at 50 °C for 1 hour. The resulting solution was diluted with EtOAc and washed with water. The organic extracts were dried with MgSO₄ and evaporated to give 190 mg (98% yield) of compound
25 **84** as a off-white viscous oil.

^1H NMR (CDCl_3) δ 1.84-1.91 (m, 1 H), 2.02-2.09 (m, 1 H), 3.08-3.14 (m, 2 H), 3.52-3.56 (m, 1 H), 4.36-4.41 (m, 1 H), 4.44-4.50 (m, 1 H), 4.60-4.67 (m, 2 H), 4.88-4.93 (m, 2 H), 7.26-7.38 (m, 7 H), 7.42-7.44 (m, 1 H), 7.79-7.81 (m, 1 H); MS m/e 352 (MH^+).

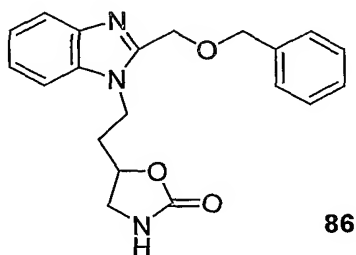
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Compound **85** was prepared from compound **84** according to the same reduction procedure described for compound **13**.

10

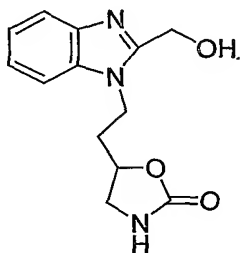
^1H NMR (CD_3OD) δ 1.86-1.94 (m, 1 H), 2.03-2.10 (m, 1 H), 2.70-2.74 (m, $J=3.2$, 12.8 Hz, 1 H), 2.84-2.88 (dd, $J=3.2$, 12.8 Hz, 1 H), 3.70-3.75 (m, 1 H), 4.44-4.54 (m, 2 H), 4.60-4.65 (m, 2 H), 4.88-4.93 (m, 2 H), 7.27-7.38 (m, 7 H), 7.59 (d, $J=8.0$ Hz, 1 H), 7.65 (d, $J=8.0$ Hz, 1 H);

15 MS m/e 326 (MH^+).

A solution of compound **85** (162 mg, 0.50 mmol), carbonyldiimidazole (89 mg, 0.55 mmol) and pyridine (198 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 hours. The mixture was diluted with CH_2Cl_2 and washed with water. The organic extracts were dried over MgSO_4 and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2 :MeOH, 40:1 to 20:1) to give 130 mg (74% yield) of compound **86** as a off-white viscous oil.

^1H NMR (CD_3OD) δ 2.16-2.21 (m, 2 H), 3.06-3.09 (m, 1 H), 3.52-3.59 (m, 1 H), 4.41-4.50 (m, 2 H), 4.58-4.65 (m, 3 H), 4.80-4.84 (m, 2 H), 7.26-7.38 (m, 6 H), 7.55-7.58 (m, 1 H), 7.82-7.85 (m, 1 H), 8.51-8.53 (m, 1 H); MS m/e 352 (MH^+).

5

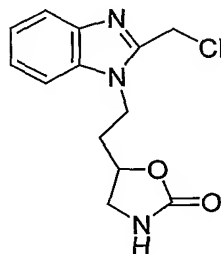


87

Compound **86** (130 mg, 0.37 mmol), palladium hydroxide on carbon (Pearlman's catalyst, 50 mg), EtOH (2 mL) and cyclohexene (1 mL) were stirred at reflux for 1 hour. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by flash column chromatography (gradient, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 30:1 to 10:1) to give 20 mg (21% yield) of compound **87** as a viscous white oil.

^1H NMR (CD_3OD) δ 2.26-2.33 (m, 2 H), 3.21-3.24 (m, 1 H), 3.65 (t, $J=8.8$ Hz, 1 H), 4.50-4.54 (m, 2 H), 4.67-4.70 (m, 1 H), 4.89-4.92 (m, 2 H), 7.24-7.34 (m, 2 H), 7.57 (d, $J=8.0$ Hz, 1 H), 7.63 (d, $J=7.9$ Hz, 1 H); MS m/e 294 (MH^+).

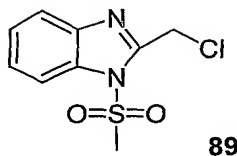
20



88

Compound **88** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

47



To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in CH_2Cl_2 (0.5 L), triethylamine
5 (136 mL, 0.97 mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated with MeOH and filtered to afford 74.9 g (64% yield) of compound **89** as a brown solid.

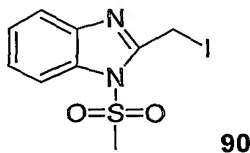
10 ^1H NMR (CDCl_3) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m, 1 H), 7.85-7.91 (m, 1 H);

IR (KBr, cm^{-1}) 3027, 2920, 1371, 1349, 1177, 1144, 1059;

MS m/e 245 (MH^+);

Anal. Calcd for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 44.18; H, 3.71; N, 11.45

15 Found: C, 44.09; H, 3.57; N, 11.49.



A solution of potassium iodide (206 g, 1.24 mol) and compound **89** (74.8
20 g, 0.414 mol) in acetone (1 L) was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in MeOH and filtered to give 83 g (60% yield) of compound **90** as a solid.

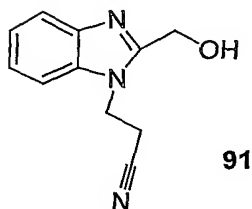
25 ^1H NMR (CDCl_3) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);

IR (KBr, cm^{-1}) 3022, 2916, 1366, 1173, 1055, 966, 763, 745;

MS m/e 336 (MH^+);

Anal. Calcd for $C_9H_9IN_2O_2S$: C, 32.16; H, 2.70; N, 8.33

Found: C, 32.05; H, 2.63; N, 8.22.



5

Compound **91** was prepared according to the Michael addition procedure described by Popov, I. I. in *Khim Geterotskl. Soedin.* **1996**, 6, 781-792.

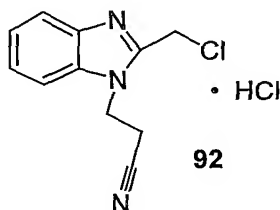
1H NMR ($CDCl_3$) δ 3.08 (t, $J = 6.8$ Hz, 2 H), 4.63 (t, $J = 6.8$ Hz, 2 H), 4.77 (d, $J = 5.7$ Hz, 2 H), 5.73 (t, $J = 5.7$ Hz, 1 H), 7.17-7.28 (m, 2 H), 7.64 (d, $J = 1.2$ Hz, 1 H), 7.70 (d, $J = 1.2$ Hz, 1 H);

MS m/e 202 (MH^+);

Anal. Calcd for $C_{11}H_{11}N_3O$: C 65.66; H, 5.51; N, 20.88

Found: C, 65.94; H, 5.57; N, 21.08.

15



Compound **92** was prepared according to the same procedure described for compound **2**.

20

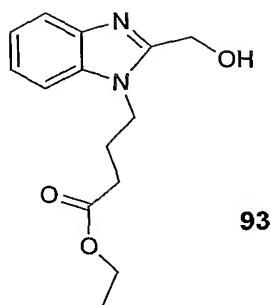
1H NMR ($CDCl_3$) δ 3.02 (t, $J = 7.0$ Hz, 2 H), 4.65 (t, $J = 7.0$ Hz, 2 H), 4.99 (s, 2 H), 7.34-7.44 (m, 3 H), 7.79-7.82 (m, 1 H);

MS m/e 220 (MH^+);

Anal. Calcd for $C_{11}H_{10}ClN_3$: C, 60.09; H, 4.65; N, 19.13

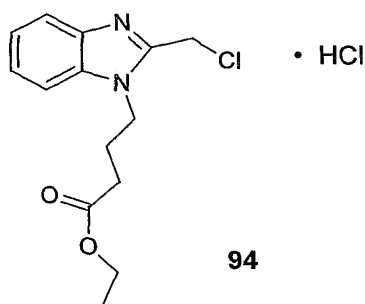
25

Found: C, 60.09; H, 4.65; N, 19.11.

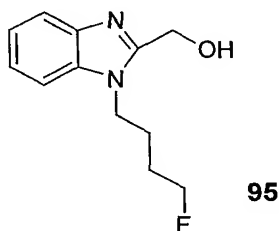


Compound **93** was prepared according to the same procedure described for
5 compound **1** except that 4-bromobutyronitrile was replaced with ethyl 4-
bromobutyrate.

¹H NMR (CDCl₃) δ 1.24 (t, J = 7.0 Hz, 3 H), 2.15-2.22 (m, 2 H), 2.38-2.42 (m, 2
H), 4.12 (q, J = 7.1 Hz, 2 H), 4.29-4.34 (m, 2 H), 4.96 (s, 2 H), 7.22-7.30 (m, 2
10 H), 7.38-7.43 (m, 1 H), 7.66-7.70 (m, 1 H);
MS m/e 250 (MH⁺).



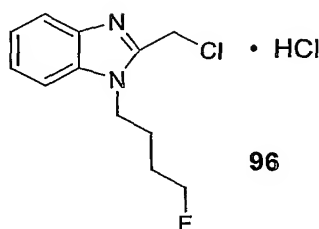
15 Compound **94** was prepared according to the same procedure described for
chloride **2** and was used immediately upon isolation.



Compound **95** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 1-bromo-4-fluorobutane.

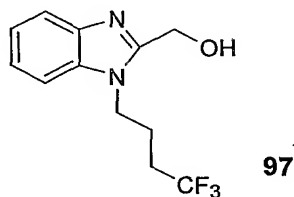
- 5 ^1H NMR (DMSO- d_6) δ 1.65-1.75 (m, 2 H), 1.85-1.90 (m, 2 H), 4.32 (t, $J = 7.5$ Hz, 2 H), 4.41 (t, $J = 6.0$ Hz, 1 H), 4.51 (t, $J = 6.0$ Hz, 1H), 4.71 (d, $J = 5.8$ Hz, 2 H), 5.62 (t, $J = 5.8$ Hz, 1 H), 7.18 (t, $J = 7.0$ Hz, 1 H), 7.23 (t, $J = 6.3$ Hz, 1 H), 7.56-7.60 (m, 2 H);
MS m/e 222 (MH^+).

10



Compound **96** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

15



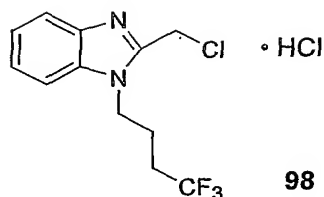
Compound **97** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 1-bromo-4,4,4-trifluorobutane.

20

^1H NMR (DMSO- d_6) δ 1.99-2.05 (m, 2 H), 2.34-2.40 (m, 2 H), 4.35-4.38 (m, 2 H), 4.73 (s, 2 H), 7.20 (t, $J = 7.2$ Hz, 1 H), 7.26 (t, $J = 7.4$ Hz, 1 H), 7.60-7.63 (m, 1 H), 7.96 (s, 1 H);

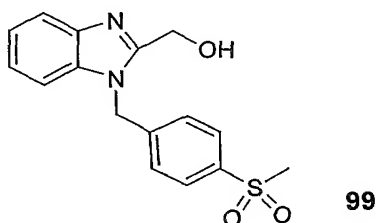
25 MS m/e 258 (MH^+).

51



Compound 98 was prepared according to the same procedure described for chloride 2 and was used immediately upon isolation.

5

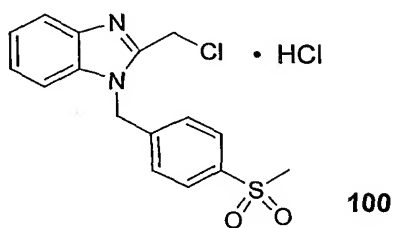


Compound 99 was prepared according to the same procedure described for compound 1 except that 4-bromobutyronitrile was replaced with 4-methylsulfonylbenzyl bromide.

^1H NMR (DMSO- d_6) δ 3.16 (s, 3 H), 4.75 (d, J = 5.6 Hz, 2 H), 5.70 (s, 2 H), 5.73-5.75 (m, 1 H), 7.17-7.21 (m, 2 H), 7.36-7.38 (m, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.64-7.65 (m, 1 H), 7.87 (d, J = 8.2 Hz, 1 H);

MS m/e 316 (MH^+).

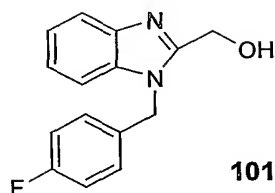
15



Compound 100 was prepared according to the same procedure described for chloride 2 and was used immediately upon isolation.

20

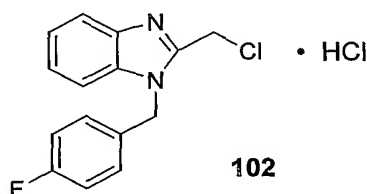
52



Compound **101** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 4-fluorobenzyl bromide.

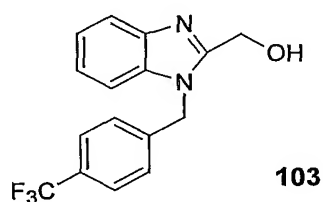
^1H NMR (DMSO- d_6) δ 4.74 (s, 2 H), 5.55 (s, 2 H), 7.13-7.18 (m, 3 H), 7.28-7.30 (m, 2 H), 7.38-7.40 (m, 1 H), 7.59-7.63 (m, 1 H);
MS m/e 256 (MH^+).

10



Compound **102** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

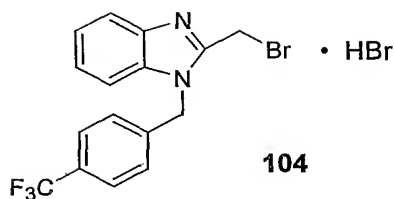
15



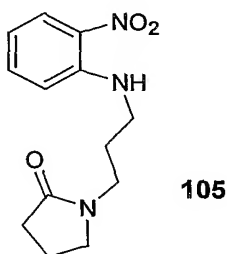
Compound **103** was prepared according to the same procedure as compound **1** except that 4-bromobutyronitrile was replaced with 4-trifluoromethylbenzyl bromide.

^1H NMR (DMSO- d_6) δ 4.74 (s, 2 H), 5.68 (s, 2 H), 7.11-7.20 (m, 2 H), 7.35-7.39 (m, 2 H), 7.62-7.64 (m, 1 H), 7.64-7.72 (m, 2 H);

MS m/e 369 (MH^+).



- 5 Compound **104** was prepared according to the same procedure described for compound **64** and was used immediately upon isolation.



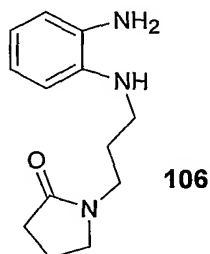
- 10 Compound **105** was prepared according to the same procedure described for compound **16** using 1-(3-aminopropyl)-2-pyrrolidinone instead of 3-(methylthio)propylamine.

1H NMR ($CDCl_3$) δ 1.93 (m, 2 H), 2.02-2.07 (m, 2 H), 2.39 (t, $J = 8.05$ Hz, 2 H),
 15 3.32-3.36 (m, 2H), 3.36-3.45 (m, 4 H), 6.64 (t, $J = 7.0$ Hz, 1 H), 6.83 (d, $J = 8.7$ Hz, 1 H), 7.42 (t, $J = 8.7$ Hz, 1 H), 8.07 (bs, 1 H), 8.16 (d, $J = 7.0$ Hz, 1 H);
 MS m/e 263 (MH^+);

Anal. Calcd for $C_{13}H_{17}N_3O_3 \cdot 0.24 H_2O$: C, 58.34; H, 6.58; N, 15.70

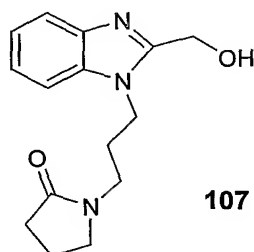
Found: C, 58.05; H, 6.20; N, 11.41.

20



Compound **106** was prepared according to the same reduction procedure described for compound **13**.

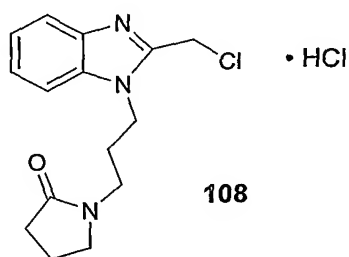
^1H NMR (CDCl_3) δ 1.83-1.88 (m, 2 H), 1.99-2.05 (m, 2 H), 2.41 (t, $J = 8.0$ Hz, 2 H), 3.16 (t, $J = 6.5$ Hz, 2 H), 3.33-3.43 (m, 4 H), 6.63-6.65 (m, 2 H), 6.70 (d, $J = 7.1$ Hz, 1 H), 6.78 (t, $J = 7.5$ Hz, 1 H), 7.26 (s, 1 H);
MS m/e 233 (MH^+).



10

Compound **107** was prepared according to the same procedure described for compound **14**.

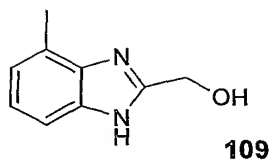
^1H NMR ($\text{DMSO}-d_6$) δ 1.87-1.92 (m, 2 H), 1.95-2.00 (m, 2 H), 2.21 (t, $J = 8.0$ Hz, 2 H), 3.25-3.34 (m, 4 H), 4.26 (t, $J = 7.6$ Hz, 2 H), 4.72 (s, 2 H), 5.65 (bs, 2 H);
MS m/e 273 (MH^+).



20

Compound **108** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

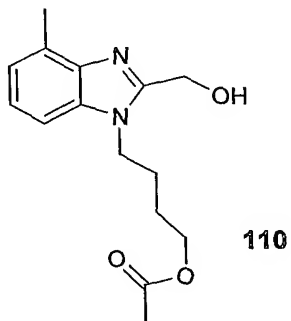
55



A mixture of 2,3-diaminotoluene (10.21 g, 83.57 mmol) and glycolic acid (9.53 g, 125.36 mmol) in 6 N HCl (100 mL) were stirred at 100 °C for 14 hours.

- 5 The reaction mixture was cooled and made basic (pH 7-8) with ammonium hydroxide. A dark brown solid was collected by filtration, washed with H₂O, and dried to give 12.47 g (92% yield) of compound **109**.

¹H NMR (DMSO-d₆) δ 2.50 (s, 3 H), 4.70 (s, 2 H), 6.93 (d, J = 7.3 Hz, 1 H), 7.04
10 (t, J = 7.6 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H).

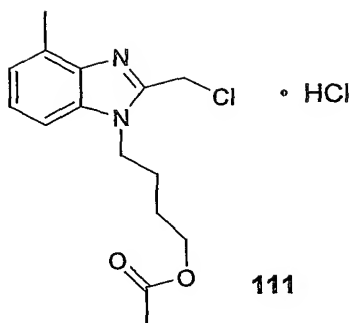


- Compound **110** was prepared according to the same procedure described
15 for compound **24** except that the base employed was cesium carbonate.

¹H NMR (CDCl₃) δ 1.67-1.73 (m, 2 H), 1.89-1.96 (m, 2 H), 2.02 (s, 3 H), 2.59 (s,
3 H), 4.05-4.10 (m, 2 H), 4.27 (t, J = 7.5 Hz, 2 H), 4.89 (s, 2 H), 7.01-7.03 (m, 1
H), 7.12-7.15 (m, 2 H);

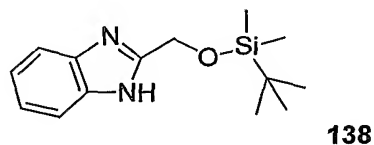
20 MS m/e 277 (MH⁺).

56



Compound 111 was prepared according to the same procedure described for chloride 2 and was used immediately upon isolation.

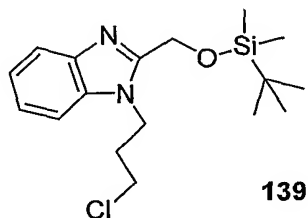
5 MS m/e 295 (MH^+).



To a solution of 2-hydroxymethylbenzimidazole (5.92 g, 40.0 mmol) and
10 imidazole (6.81 g, 100.0 mmol) in THF (100 mL) was added *t*-butyldimethylsilyl
chloride (12.65 g, 84.0 mmol) in several portions. The resulting mixture was
stirred at room temperature for 2 hours and filtered. The filtrate was diluted with
EtOAc and washed with H₂O and brine. The organic layer was dried over MgSO₄
and evaporated. The residue was recrystallized from hexanes/EtOAc to give 8.50
15 g (81%) of compound 138 as white needles.

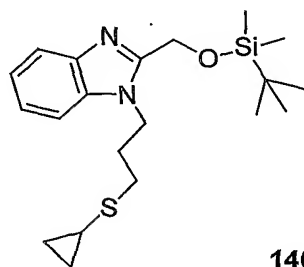
¹H NMR (CDCl₃) δ 0.15-0.16 (m, 6 H), 0.95-0.97 (m, 9 H), 5.02-5.03 (m, 2 H),
7.24-7.27 (m, 2 H), 7.59 (bs, 2 H);
MS m/e 263 (MH^+).

20



Compound **139** was prepared according to the same procedure described for compound **68** except that cesium carbonate was used instead of sodium hydride as the base.

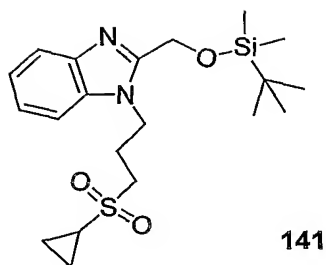
- 5 ^1H NMR (CDCl_3) δ 0.13-0.14 (m, 6 H), 0.91-0.92 (m, 9 H), 2.35-2.37 (m, 2 H), 3.58 (t, $J = 6.0$ Hz, 2 H), 4.50 (t, $J = 7.0$ Hz, 2 H), 5.01 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.77 (d, $J = 10.0$ Hz, 1 H); MS m/e 339 (MH^+).



- Compound **140** was prepared through the coupling of compound **139** and cyclopropylsulfide according to the same procedure described for compound **74** except using cesium carbonate instead of sodium hydride as the base. The
- 15 cyclopropylsulfide was prepared according to a literature procedure by E. Block, A. Schwan, and D. Dixon in *Journal of the American Chemical Society*, **1992**, *114*, 3492-3499.

- ^1H NMR (CDCl_3) δ 0.12-0.13 (m, 6 H), 0.54-0.56 (m, 2 H), 0.84-0.86 (m, 2 H),
- 20 0.90-0.91 (m, 9 H), 1.87-1.92 (m, 1 H), 2.20-2.25 (m, 2 H), 2.62 (t, $J = 7.0$ Hz, 2 H), 4.43 (t, $J = 7.4$ Hz, 2 H), 5.00 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.77 (d, $J = 10.0$ Hz, 1 H); MS m/e 377 (MH^+).

58

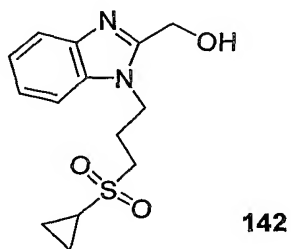


Compound **141** was prepared from compound **140** by the same procedure described for compound **18**.

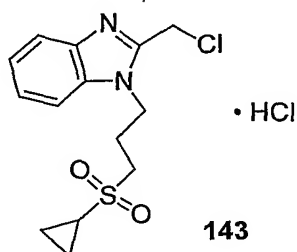
5

^1H NMR (CDCl_3) δ 0.13-0.14 (m, 6 H), 0.91-0.92 (m, 9 H), 1.01-1.03 (m, 2 H), 1.23-1.24 (m, 2 H), 2.31-2.34 (m, 1 H), 2.48-2.52 (m, 2 H), 3.07 (t, $J = 7.2$ Hz, 2 H), 4.51 (t, $J = 7.1$ Hz, 2 H), 5.00 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.77 (d, $J = 10.0$ Hz, 1 H);

10 MS m/e 409 (MH^+).



To solution of compound **141** (27 mg, 0.07 mmol) in THF (0.5 mL) was added TBAF (1 M THF solution, 0.13 mL, 0.13 mmol) at 0 °C and the mixture was stirred for 10 minutes. The solvent was evaporated and the residue was passed through a short plug of silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1) to give crude compound **142** which was used immediately upon isolation.

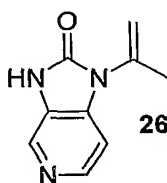


20

Compound **143** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.

II. Preparation of 2-Oxo-imidazopyridines and 2-Oxo-imidazopyrimidines:

Compounds **26-58** and **112-126** are intermediates prepared according to the procedures depicted in Scheme III.

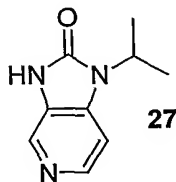


10

3,4-Diaminopyridine (30 g, 274.9 mmol), ethyl acetoacetate (53.66 g, 412 mmol) and DBU (1 mL) were stirred at reflux in xylene (300 mL) under a Dean-Stark trap. After stirring for 3.5 hours, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc; EtOAc:MeOH = 10:1) to give a solid which was recrystallized from CH₂Cl₂/EtOAc to afford **26** (21.45 g, 45% yield) as white crystals.

¹H NMR (CDCl₃) δ 2.19 (s, 3 H), 5.22 (s, 1 H), 5.46 (s, 1 H), 7.19 (d, J = 5.4 Hz, 1 H), 8.20 (d, J = 5.4 Hz, 1 H), 8.23 (s, 1 H); MS m/e 176 (MH⁺).

20

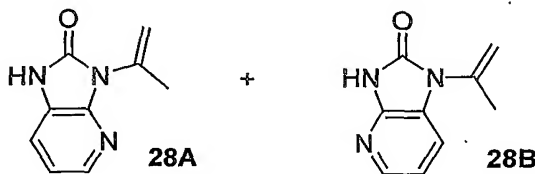


25

Compound **26** (1.0 g, 5.71 mmol) in the presence of 10 % palladium on carbon (0.1 g) in MeOH (10 mL) was hydrogenated in a Parr shaker at 40 psi for

2 days. The catalyst was removed by filtration and the filtrate was evaporated to give compound **27** as a white solid.

^1H NMR (CDCl_3) δ 1.57 (d, $J = 7.0$ Hz, 6 H), 4.72-4.76 (m, 1 H), 7.19 (d, $J = 5.8$ Hz, 1 H), 8.30 (d, $J = 5.8$ Hz, 1 H), 8.58 (s, 1 H);
MS m/e 178 (MH^+).



10 The same procedure described for compound **26** was carried out using 2,3-diaminopyridine to give **28A** and **28 B** which were separated by flash chromatography (gradient, CH_2Cl_2 /acetone, 5:1 to 4:1).

Compound **28A**

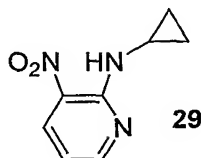
15

^1H NMR (CD_3OD) δ 2.31 (s, 3 H), 5.40 (s, 1 H), 5.51 (s, 1 H), 7.04 (dd, $J = 5.2$, 7.7 Hz, 1 H), 7.38 (dd, $J = 1.4$, 7.7 Hz, 1 H), 8.09 (dd, $J = 1.4$, 5.2 Hz, 1 H);
MS m/e 176 (MH^+).

20 Compound **28B**

^1H NMR (CD_3OD) δ 2.26 (s, 3 H), 5.21 (s, 1 H), 5.38 (s, 1 H), 7.11 (dd, $J = 5.5$, 7.9 Hz, 1 H), 7.40 (dd, $J = 1.3$, 7.9 Hz, 1 H), 8.09 (dd, $J = 1.3$, 5.5 Hz, 1 H);
MS m/e 176 (MH^+).

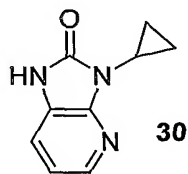
25



2-Chloro-3-nitropyridine (7.0 g, 50.0 mmol), cyclopropylamine (3.71 g, 65 mmol) and potassium carbonate (13.82 g, 100 mmol) were stirred in CH₃CN (100 mL) at room temperature overnight and at reflux for an additional hour.

The solid was filtered and the filtrate was evaporated. Water was added to the residue and the mixture was extracted with EtOAc. The combined extracts were dried over MgSO₄ and filtered. Evaporation of the solvent gave **29** (8.40 g, 94% yield) as a dark brown solid.

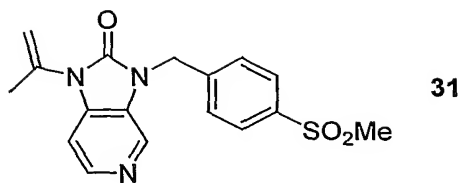
¹H NMR (CD₃OD) δ 0.63-0.69 (m, 2 H), 0.93-0.97 (m, 2 H), 3.01-3.06 (m, 1 H), 6.70-6.72 (dd, J = 4.5, 8.3 Hz, 1 H), 8.24 (bs, 1 H), 8.42 (dd, J = 1.7, 8.3 Hz, 1 H), 8.52 (dd, J = 1.7, 4.5 Hz, 1 H); MS m/e 180 (MH⁺).



15

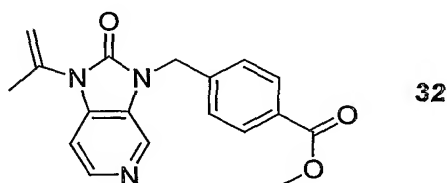
Compound **29** (8.29 g, 46.28 mmol) was reduced with iron using the procedure described for compound **7**. To the crude diamine in THF (50 mL) was added 1 equivalent of carbonyldiimidazole and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was diluted with CH₂Cl₂, washed with water, dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc / hexane, 1:1 to EtOAc / MeOH, 10: 1) to give **30** (1.93 g, 24 % yield over two steps) as a light orange solid.

¹H NMR (CDCl₃) δ 1.19 (d, J = 3.4 Hz, 2 H), 1.20 (s, 2H), 3.01-3.04 (m, 2 H), 7.02 (dd, J = 5.3, 7.7 Hz, 1 H), 7.32 (dd, J = 1.4, 7.7 Hz, 1 H), 8.12 (dd, J = 1.4 Hz, 5.3 Hz, 1 H), 9.61 (bs, 1 H); MS m/e 176 (MH⁺).



A mixture of **26** (2.0 g, 11.4 mmol), Cs₂CO₃ (5.58 g, 17.1 mmol) and *p*-methylsulfonylbenzyl chloride (2.34 g, 11.4 mmol) in acetone (50 mL) was stirred at reflux for 2 hours. The solid was removed by filtration and the filtrate was evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) to afford **31** (3.24 g, 83% yield) as a white solid.

¹HNMR (DMSO-d₆) δ 2.18 (s, 3 H), 3.20 (s, 3 H), 5.23 (s, 2 H), 5.26 (s, 1 H), 5.45 (d, J = 1.2 Hz, 1 H), 7.21 (d, J = 5.3 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.92 (d, J = 8.4 Hz, 2 H), 8.25 (d, J = 5.1 Hz, 1H), 8.41 (s, 1 H); MS m/e 344 (MH⁺).

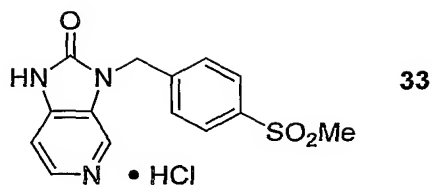


15

Compound **32** was prepared using the same procedure for compound **31**, except that methylsulfonylbenzyl chloride was replaced with methyl *p*-bromomethylbenzoate.

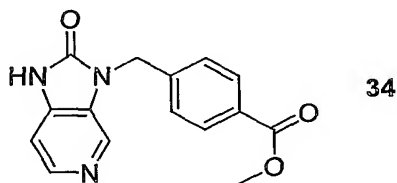
¹HNMR (DMSO-d₆) δ 2.05 (s, 3H), 3.70 (s, 3H), 5.06 (s, 2H), 5.12 (s, 1H), 5.32 (d, J=1.4 Hz, 1H), 7.07-7.09 (dd, J= 0.45, 5.4 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.80-7.82 (m, 2H), 8.11 (d, J=5.3 Hz, 1H), 8.23 (s, 1H); MS m/e 324 (MH⁺).

63



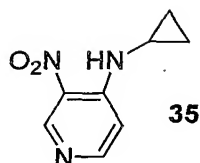
A solution of **31** (3.24 g, 9.45 mmol) in concentrated HCl (5 ml) and MeOH (50 ml) was stirred at reflux for 2 hours. The solvent was evaporated and the residue was triturated in hot MeOH to yield **33** (2.80 g, 87% yield) as a white solid as the HCl salt.

¹H NMR (DMSO-d₆) δ 3.18 (s, 3 H), 5.17 (s, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.91 (d, J = 8.2 Hz, 2 H), 8.17 (d, J = 5.0 Hz, 1 H), 8.29 (s, 1 H);
MS m/e 304 (MH⁺).



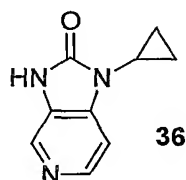
A solution of **32** (1.30 g, 4.02 mmol) in concentrated HCl (10 ml) and MeOH (10 ml) was stirred at reflux for 1 hour. The solution was neutralized with K₂CO₃ to pH 6, and extracted with EtOAc. The organic layer was dried and evaporated to dryness. The crude product was triturated with hot CH₂Cl₂ to yield **34** (0.85 g, 75% yield) as off-white solid.

¹H NMR (DMSO-d₆) δ 3.90 (s, 3 H), 5.20 (s, 2 H), 7.13 (d, J = 5.2 Hz, 1 H), 7.53 (d, J = 8.2 Hz, 2 H), 8.00 (d, J = 8.2 Hz, 2 H), 8.22 (d, J = 5.2 Hz, 1 H), 8.31 (s, 1 H);
MS m/e 284 (MH⁺).



A solution of 4-methoxy-3-nitro-pyridine (7.71 g, 50 mmol) and
5 cyclopropylamine (7.14g, 125 mmol) in EtOH (20 mL) was stirred at reflux
under a dry-ice trap condenser for 2 hours. The solvent was evaporated to give
35 as a yellow solid.

^1H NMR (CD_3OD) δ 0.72-0.75 (m, 2 H), 0.99-1.03 (m, 2 H), 2.63-2.68 (m, 1 H),
10 7.19 (d, $J = 6.2$ Hz, 1 H), 8.26 (bs, 1 H), 8.35 (d, $J = 6.2$ Hz, 1 H), 9.22 (s, 1 H);
IR (KBr, cm^{-1}) 3369, 1613, 1560, 1515, 1406, 1254, 1195, 1039, 881, 846, 769, 545;
MS m/e 180 (MH^+).



15

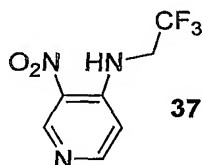
To a solution of **35** (12.28 g, 68.6 mmol) in anhydrous MeOH (120 mL)
was added 10% palladium on carbon (3 g) in several portions under nitrogen.
The reduction was carried out using a balloon containing hydrogen (1 atm) for 16
hours. The catalyst was removed by filtration through a pad of Celite and rinsed
20 with MeOH. The filtrate was concentrated to a slurry and Et_2O was added to
precipitate the diamine product as a light yellow solid (10.1g, 99% yield).

To a slurry of the diamine and polyvinylpyridine (22.0 g) in acetonitrile
(70 mL) of a 20% phosgene solution in toluene was added dropwise (70 mL,
25 135.4 mmol). After stirring at room temperature for 2 hours, the reaction was
quenched with water. Polyvinylpyridine was removed by filtration and rinsed

with MeOH. The filtrate was concentrated and Et₂O was added to precipitate product **36** (15.5g, 98% yield) as a light brown solid.

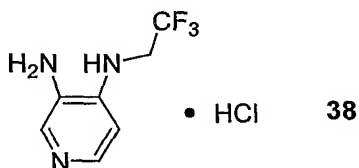
¹H NMR (CD₃OD) δ 0.95-0.98 (m, 2 H), 1.07-1.14 (m, 2 H), 2.91-2.96 (m, 1 H),
5 7.32 (dd, J = 0.5, 5.3 Hz, 1 H), 7.18 (s, 1 H), 8.21 (d, J = 5.3 Hz, 1 H);
MS m/e 176 (MH⁺).

2-Oxo-imidazopyridine **39** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced
10 with 2 equivalents of trifluoroethylamine hydrochloride and diisopropylethylamine, and the reaction was carried out in a sealed tube at 120-130 °C for 2 days.



15 ¹H NMR (CDCl₃) δ 4.02 (q, J = 7.9 Hz, 2 H), 6.83 (d, J = 5.5 Hz, 1 H), 8.43 (d over bs, 2 H), 9.28 (s, 1 H);
IR (KBr, cm⁻¹): 3287, 3241, 1629, 1611, 1363, 1254, 1150, 1047, 870;
MS m/e 222 (MH⁺);

20 Anal. Calcd for C₇H₆F₃N₃O₂ : C, 38.02; H, 2.73; N, 19.00
Found: C, 38.00; H, 2.69; N, 19.19.

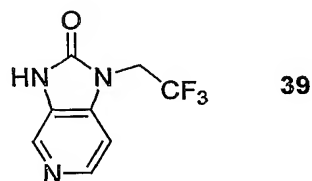


25 ¹H NMR (CD₃OD) δ 4.23 (q, J = 9.0 Hz, 2 H), 7.05 (d, J = 6.6 Hz, 1 H), 7.74 (d, J = 1.1 Hz, 1 H), 7.84 (d, J = 1.1, 6.6 Hz, 1 H);
IR (KBr, cm⁻¹): 3343, 3202, 3062, 1625, 1578, 1529, 1257, 1154, 949;

MS m/e 192 (MH^+);

Anal. Calcd for $\text{C}_7\text{H}_8\text{F}_3\text{N}_3 \cdot \text{HCl}$: C, 36.94; H, 3.99; N, 18.46

Found: C, 37.19; H, 3.86; N, 18.79.



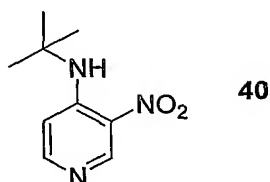
^1H NMR (DMSO-d_6) δ 4.99 (q, $J = 9.2$ Hz, 2 H), 7.90 (d, $J = 6.3$ Hz, 1 H), 8.61 (d, $J = 6.3$ Hz, 1 H), 8.63 (s, 1 H);

IR (KBr, cm^{-1}): 3423, 2994, 1744, 1517, 1347, 1254, 1263, 1173, 1000, 811;

10 MS m/e 218 (MH^+).

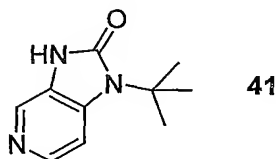
2-Oxo-imidazopyridine **41** was prepared using the same procedure described for compound **36**, except that cyclopropylamine was replaced with *t*-butylamine and the reaction was carried out in a sealed tube at 80 °C. This

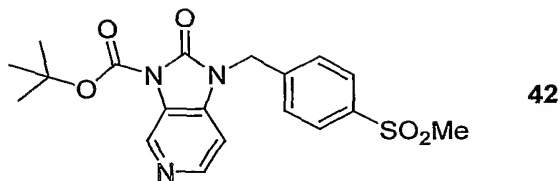
15 compound was used as a crude intermediate for the coupling reaction.



^1H NMR (CDCl_3) δ 1.54 (s, 9 H), 7.21 (d, $J = 6.3$ Hz, 1 H), 8.17 (d, $J = 6.3$ Hz, 1 H), 9.08 (s, 1 H);

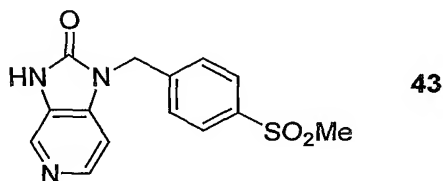
MS m/e 196 (MH^+).





A mixture of 1,2-dihydro-2-oxo-3H-imidazol[4,5-c]pyridine-3-carboxylic acid, 1,1-dimethyl ethyl ester (470 mg, 2.0 mmol) (prepared according to the procedure described by N. Meanwell et al. in *J. Org. Chem.* **1995**, *60*, 1565), Cs₂CO₃ (978 mg, 3.0 mmol) and *p*-methylsulfonylbenzyl chloride (451 mg, 2.2 mmol) in acetone (10 mL) was stirred at reflux for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20 :1) to afford **42** (500 mg, 62% yield) as a white solid.

¹H NMR (CDCl₃) δ 1.71 (s, 9 H), 3.04 (s, 3 H), 5.15 (s, 2 H), 6.90 (m, 1 H), 7.54 (m, 2 H), 7.93 (m, 2 H), 8.40 (m, 1 H), 9.01 (m, 1 H); MS m/e 404 (MH⁺).

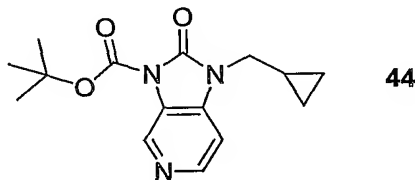


A mixture of **42** (260 mg, 0.64 mmol) and 1 N NaOH (3.22 ml) in THF (5 ml) and water (1 ml) was stirred at the ambient temperature overnight. The mixture was diluted with saturated NH₄Cl and extracted with CH₂Cl₂. The combined extracts were dried over MgSO₄ and evaporated. The residue was triturated with EtOAc to produce **43** (180 mg, 93% yield) as a white solid.

¹H NMR (DMSO-d₆) δ 3.34 (s, 3 H), 5.16 (s, 2 H), 7.19 (d, J = 5.2 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.89 (d, J = 8.4 Hz, 2 H), 8.15 (d, J = 5.2 Hz, 1 H), 8.22 (s, 1 H), 11.34 (s, 1 H); MS m/e 304 (MH⁺).

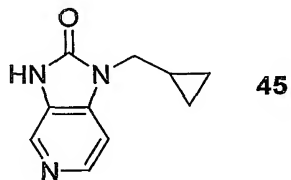
2-Oxo-imidazopyridine **45** was prepared using the same procedure for compound **43**, except that *p*-methylsulfonylbenzyl chloride was replaced with cyclopropylmethyl bromide. This compound was used as a crude intermediate for the coupling reaction.

5



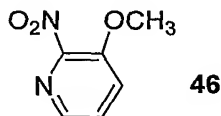
^1H NMR (CD_3OD) δ 0.44-0.45 (m, 2 H), 0.56-0.58 (m, 2 H), 1.21-1.25 (m, 1 H), 1.69 (s, 9 H), 3.79 (d, $J = 7.1$ Hz, 2 H), 7.35 (d, $J = 5.4$ Hz, 1 H), 8.34 (d, $J = 5.4$ Hz, 1 H), 8.84 (s, 1 H);
MS m/e 290 (MH^+).

10



^1H NMR (CD_3OD) δ 7.54 (d, $J = 1.2$ Hz, 1 H), 8.19 (d, $J = 1.2$ Hz, 1 H), 8.23 (s, 1 H), 8.67 (s, 1 H);
MS m/e 137 (MH^+).

15



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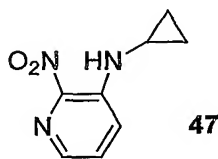
To a solution of 3-hydroxy-2-nitropyridine (100 g, 0.71 mol) in acetone (800 mL) was added potassium carbonate (148 g, 1.07 mol) followed by dimethyl sulfate (99 g, 0.79 mol). The reaction mixture was stirred vigorously using a mechanical stirrer and heated to 60 °C for 4.5 hours. The mixture was
25 filtered while still warm. The filtrate was stripped of solvent to give a crude

brown solid. The solid was diluted with water and extracted with EtOAc. The organic extracts were dried over anhydrous MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 1:1) to give **46** as a bright yellow solid (81 g, 74 % yield).

5

^1H NMR (CDCl_3) δ 3.98 (s, 3 H), 7.51-7.57 (m, 2 H), 8.10 (dd, $J = 1.5, 7.5$ Hz, 1 H);

MS m/e 155 (MH^+).



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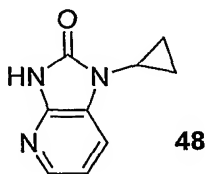
Compound **47** was obtained from **46** using the same procedure for the preparation of **35** except that the reaction was carried out with 1.5 equivalents of cyclopropylamine in a sealed tube at 120 °C for 2 days.

15

^1H NMR (CDCl_3) δ 0.67-0.72 (m, 2 H), 0.89-1.00 (m, 2 H), 2.58-2.65 (m, 1 H), 7.50 (dd, $J = 4.0, 8.6$ Hz, 1 H), 7.82 ($J = 8.6$ Hz, 1 H), 7.83 (d, $J = 8.6$ Hz, 1 H), 7.97 (dd, $J = 1.4, 4.0$ Hz, 1 H);

MS m/e 155 (MH^+).

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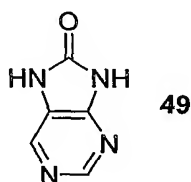


A solution of **47** (300 mg, 1.67 mmol) in MeOH (25 mL) was agitated under H_2 (10 psi) in the presence of 10% palladium on carbon (60 mg) for 15 min. The catalyst was removed by filtration through a pad of Celite. To the filtrate was added urea (402 mg, 6.70 mmol), and the mixture was evaporated. The solid residue was then heated at 170 °C for 16 hours. The resulting black

25

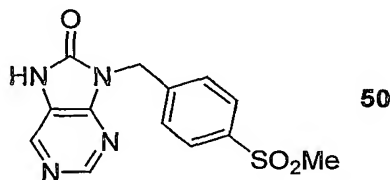
solid was heated in boiling ethanol and filtered. The filtrate was evaporated and the residue was purified by flash chromatography (gradient, straight CH₂Cl₂ to CH₂Cl₂/MeOH, 20:1) to give compound **48** as a yellow solid (82 mg, 28% yield).

- 5 ¹H NMR (CDCl₃) δ 0.99-1.04 (m, 2 H), 1.12-1.15 (m, 2 H), 2.89-2.93 (m, 1 H), 7.05 (dd, J = 5.3, 7.8 Hz, 1 H), 7.41 (dd, J = 1.3; 7.8 Hz, 1 H), 8.05 (d, J = 5.3 Hz, 1 H);
MS m/e 176 (MH⁺).



10

Compound **49** was prepared from 4,5-diaminopyrimidine and urea using the same procedure described for compound **48**.

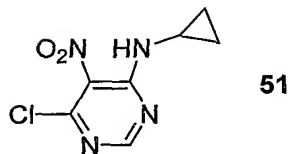


15

- To a slurry of **49** (136 mg, 1.0 mmol) in THF (5 mL) was added BTPP (946 mg, 3.0 mmol) and *p*-methylsulfonylbenzyl chloride (205 mg, 1.0 mmol) at ambient temperature. After stirring overnight, the solution was diluted with
20 EtOAc, washed with water, dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) to afford compound **50** (52 mg, 34% yield) as a white solid.

- 25 ¹H NMR (CD₃OD) δ 3.08 (s, 3 H), 5.26 (s, 2 H), 7.67 (d, J = 8.4 Hz, 2 H), 7.91-7.93 (m, 2 H), 8.34 (s, 1 H), 8.74 (s, 1 H);
MS m/e 305 (MH⁺).

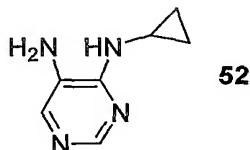
71



To a suspension of 4,6-dichloro-5-nitropyrimidine (3.88 g, 20.0 mmol) and triethylamine (4.05 g, 40.0 mmol) in THF (50 ml) was added
5 cyclopropylamine (1.14 g, 20.0 mmol) dropwise at 0 °C. After stirring at 0 °C for 2 hours, the slurry was filtered. The filtrate was diluted with EtOAc, washed with water, dried over MgSO₄, and evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 100:1 to 40:1) to afford compound **51** (2.75 g, 64% yield) as a yellow solid.

10

¹H NMR (DMSO-d₆) δ 0.61-0.64 (m, 2 H), 0.74-0.78 (m, 2 H), 2.92 (bs, 1 H), 8.43 (bs, 1 H), 8.51 (s, 1 H);
MS m/e 215 (MH⁺).



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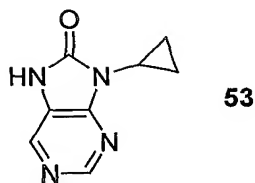
Pyrimidine **51** was reduced using catalytic hydrogenation with 10 % palladium on carbon in MeOH at 40 psi (Parr shaker) for 1 hour to afford compound **52**.

20

¹H NMR (DMSO-d₆) δ 0.74-0.76 (m, 2 H), 0.79-0.83 (m, 2 H), 3.06-3.11 (m, 1 H), 6.17 (bs, 2 H), 7.47 (d, J = 1.5 Hz, 1 H), 8.37 (d, J = 1.0 Hz, 1 H), 9.09 (d, J = 3.8 Hz, 1 H);
MS m/e 151 (MH⁺).

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72



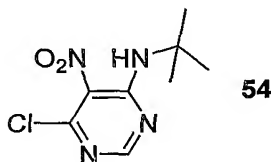
Compound **53** was obtained by cyclization of diamine **52** according to the same procedure described for compound **36** using phosgene and polyvinylpyridine.

^1H NMR (CD_3OD) δ 1.14-1.19 (m, 2 H), 1.20-1.27 (m, 2 H), 3.11-3.18 (m, 1 H), 8.47 (d, $J = 0.45$ Hz, 1 H), 9.01 (s, 1 H); MS m/e 177 (MH^+).

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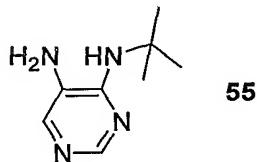
2-Oxo-imidazopyrimidine **56** was prepared using the same procedure for compound **53**, except that cyclopropylamine was replaced with *t*-butylamine. The compound was used as a crude intermediate for the coupling reaction without further purification.

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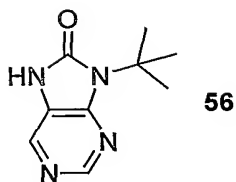
^1H NMR (CDCl_3) δ 1.52 (s, 9 H), 7.26 (bs, 1 H), 8.37 (s, 1 H); MS m/e 231 (MH^+).

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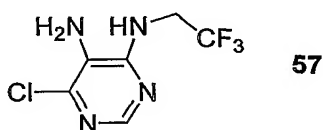


^1H NMR (CD_3OD) δ 1.57 (s, 9 H), 7.49 (d, $J = 1.3$ Hz, 1 H), 8.27 (d, $J = 1.3$ Hz, 1 H); MS m/e 167 (MH^+).

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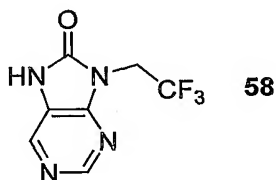


2-Oxo-imidazopyrimidine **58** was prepared according to the same
5 procedure described for compound **53**, except that cyclopropylamine was
replaced with 2,2,2-trifluoroethylamine. The crude intermediate was used in the
coupling reaction without further purification.



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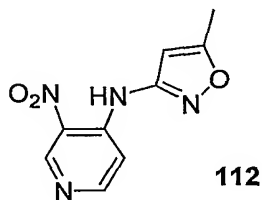
^1H NMR (CD_3OD) δ 4.30-4.36 (m, 2 H), 8.46 (s, 1 H);
MS m/e 226 (MH^+).



15

2-Oxo-imidazopyridine **113** was prepared according to the same
procedure for the preparation of **36**, except that cyclopropylamine was replaced
with 2 equivalents of 3-amino-5-methylisoxazole, and the reaction was carried
out in MeOH at 100 °C for 18 hours in a sealed pressure tube.

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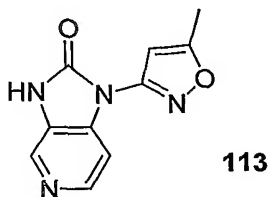


^1H NMR (CD_3OD) δ 0.88 (s, 3 H), 4.71 (s, 1 H), 6.79 (d, $J = 6.2$ Hz, 1 H), 6.95 (d, $J = 6.2$ Hz, 1 H), 7.69 (d, 1 H);

IR (KBr, cm^{-1}) 3323, 3125, 3097, 1604, 1581, 1521, 1499, 1228, 1179;

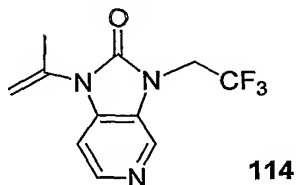
MS m/e 221 (MH^+);

- 5 Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_4\text{O}_3$: C, 49.09; H, 3.66; N, 25.44
 Found: C, 49.04; H, 3.63; N, 25.06.



- 10 ^1H NMR (CD_3OD) δ 2.50 (s, 3 H), 6.94 (s, 1 H), 7.95 (dd, $J = 0.6, 6.55$ Hz, 1 H), 8.31 (s, 1 H), 8.32 (d, $J = 5.5$ Hz, 1 H);
IR (KBr, cm^{-1}) 3546, 3463, 2679, 1744, 1720, 1596, 1474, 1457, 1193, 1129, 809, 633;
MS m/e 217 (MH^+).

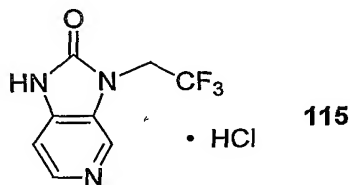
15



- A mixture of compound **26** (400 mg, 2.28 mmol) and BTPP (1.57 g, 5.02 mmol) in THF (10 mL) was stirred for 20 minutes after which 2,2,2-trifluoroethyl *p*-toluenesulfonate (605 mg, 2.40 mmol) was added to the mixture. The reaction mixture was stirred at 45 °C for 18 hours and then at 60 °C for an additional 24 hours. The solvent was evaporated and the residue was diluted with H_2O and extracted with EtOAc. The combined organic extracts were dried over MgSO_4 and evaporated. Purification by flash column chromatography (EtOAc/MeOH, 20:1) gave 295 mg (50% yield) of **114** as a white solid.
- 25

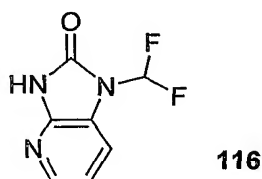
^1H NMR (CDCl_3) δ 2.24 (s, 3 H), 4.51 (q, $J = 8.6$ Hz, 2 H), 5.24 (s, 1 H), 5.43 (d, $J = 1.1$ Hz, 1 H), 7.10 (d, $J = 5.5$ Hz, 1 H), 8.39 (s, 1 H), 8.40 (d, $J = 5.5$ Hz, 1 H);
IR (KBr, cm^{-1}) 3026, 1727, 1605, 1503, 1169, 1156, 1126, 827;
MS m/e 258 (MH^+).

5



Compound **114** (272 mg, 1.06 mmol) and concentrated HCl (12 mL) in MeOH (20 mL) were refluxed for 72 hours. The solvent was evaporated and the
10 residue was dried under vacuum to give 263 mg (99% yield) of compound **115** as the HCl salt.

^1H NMR ($\text{DMSO}-d_6$) δ 4.93 (q, $J = 9.2$ Hz, 2 H), 7.61 (d, $J = 6.3$ Hz, 1 H), 8.54 (d, $J = 6.3$ Hz, 1 H), 8.89 (s, 1 H);
15 MS m/e 218 (MH^+).



Compound **28B** (1.2 g, 6.86 mmol) and BTPP (3.21 g, 10.28 mmol) in
20 CH_2Cl_2 were mixed together in a sealed flask and cooled to -78°C .
Chlorodifluoromethane (gas, approximately 2 g, 23.26 mmol) was bubbled into the solution in the sealed flask. The flask was sealed and the temperature was raised to 0°C for 10 minutes and then to room temperature for 3 minutes. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 . The
25 combined extracts were dried over MgSO_4 and evaporated. To the residue was added 6 N HCl in MeOH (1:1 mixture, 10 mL). The mixture was stirred at reflux for 6 hours. The reaction was neutralized with solid Na_2CO_3 . The solvent was

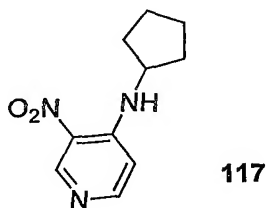
concentrated and the resulting aqueous solution was extracted with CH₂Cl₂. The combined extracts were dried over MgSO₄ and evaporated. Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) gave 398 mg (31% yield) of **116**.

5

¹H NMR (CDCl₃) δ 7.14 (dd, J = 5.7, 7.4 Hz, 1 H), 7.36 (t, J = 58.7 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 8.21 (d, J = 5.3 Hz, 1 H), 9.40 (bs, 1 H); MS m/e 186 (MH⁺).

10

Compound **119** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of cyclopentylamine, and the reaction was carried out in a sealed pressure tube at 120 °C for 2 hours.

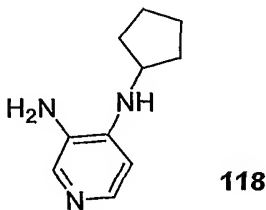


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¹H NMR (CDCl₃) δ 1.62-1.69 (m, 2 H), 1.70-1.76 (m, 2 H), 1.79-1.85 (m, 2 H), 2.10-2.16 (m, 2 H), 3.96-4.01 (m, 1 H), 6.76 (d, J = 6.2 Hz, 1 H), 8.23 (bs, 1 H), 8.27 (d, J = 6.2 Hz, 1 H), 9.21 (s, 1 H);

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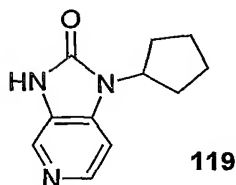
MS m/e 208 (MH⁺).



¹H NMR (CDCl₃) δ 1.48-1.53 (m, 2 H), 1.61-1.64 (m, 2 H), 1.69-1.74 (m, 2 H), 2.00-2.06 (m, 2 H), 3.12 (bs, 2 H), 3.77-3.83 (m, 1 H), 4.22 (bd, J = 4.5 Hz, 1 H), 6.47 (d, J = 5.4 Hz, 1 H), 7.85 (s, 1 H), 7.92 (d, J = 5.4 Hz, 1 H);

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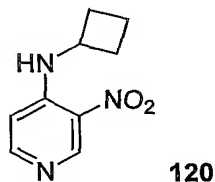
MS m/e 178 (MH^+).



- 5 1H NMR ($DMSO-d_6$) δ 1.61-1.68 (m, 2 H), 1.85-1.95 (m, 4 H), 1.97-2.02 (m, 2 H), 4.11 (bs, 1 H), 4.67-4.74 (m, 1 H), 7.20 (d, $J = 5.3$ Hz, 1 H), 8.16 (d, $J = 5.4$ Hz, 1 H), 8.19 (s, 1 H);

MS m/e 204 (MH^+).

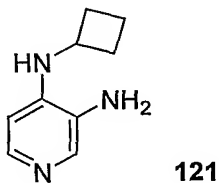
- 10 Compound 122 was prepared using the same procedure described for the preparation of 36, except that cyclopropylamine was replaced with 2 equivalents of cyclobutylamine, and the reaction was carried out in a sealed pressure tube at 100 °C.



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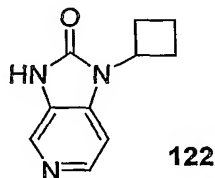
1H NMR ($CDCl_3$) δ 1.89-1.97 (m, 2 H), 2.05-2.09 (m, 2 H), 2.50-2.56 (m, 2 H), 4.06-4.13 (m, 1 H), 6.56-6.62 (m, 1 H), 8.23 (s, 1 H), 8.27 (d, $J=5.6$ Hz, 1 H), 9.21 (s, 1 H);

- 20 MS m/e 194 (MH^+).

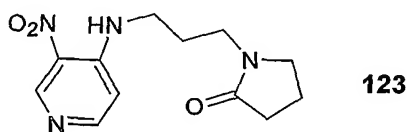


^1H NMR (DMSO-d_6) δ 1.70-1.79 (m, 2 H), 1.83-1.91 (m, 2 H), 2.32-2.50 (m, 2 H), 3.85-3.91 (m, 1 H), 4.59 (s, 2 H), 5.49 (d, $J=6.2$ Hz, 1H), 6.22 (d, $J=5.3$ Hz, 1 H), 7.55 (d, $J= 5.2$ Hz, 1 H), 7.63 (s, 1 H);
MS m/e 164 (MH^+).

5



^1H NMR (CD_3OD) δ 1.92-2.04 (m, 2 H), 2.43-2.49 (m, 2 H), 2.88-2.97 (m, 2 H), 4.93-4.98 (m, 1 H), 7.83 (d, $J= 6.6$ Hz, 1 H), 8.41-8.43 (m, 2 H);

10 MS m/e 190 (MH^+).

To a solution of 4-chloro-3-nitropyridine (4.9 g, 30.80 mmol) and 1-(3-aminopropyl)-2-pyrrolidinone (4.4 g, 30.80 mmol) in CH_3CN (50 mL) was added K_2CO_3 (4.25 g, 30.8 mmol) and the mixture was stirred for 8 hours. Additional 1-(3-aminopropyl)-2-pyrrolidinone (0.2 g, 1.41 mmol) was added and the mixture was stirred for 24 hours at room temperature. The mixture was filtered and concentrated to give 8.0 g (98% yield) of the compound **123** as an orange oil.

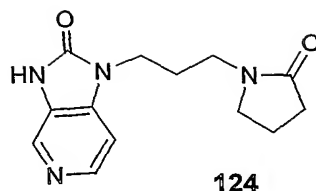
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^1H NMR (CDCl_3) δ 1.89-1.99 (m, 2 H); 2.02-2.15 (m, 2 H), 2.35 (t, $J = 8.05$ Hz, 2 H); 3.36-3.47 (m, 6 H), 6.70 (d, $J = 6.2$ Hz, 1 H), 8.28 (d, $J = 6.27$ Hz, 1 H), 8.37-8.40 (s, 1 H), 9.20 (s, 1 H);

MS m/e 264 (MH^+).

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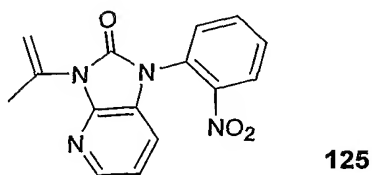
79



A mixture of **123** (2.0 g, 7.6 mmol) and 10% palladium on carbon (200 mg) in EtOH (50 mL) was hydrogenated at 50 psi for 18 hours, filtered and concentrated to give 1.6 g (90% yield) of the diamine as a black oil. The oil was dissolved in CH₂Cl₂ (40 mL), treated with carbonyl diimidazole (1.22 mg, 7.5 mmol) and stirred for 12 hours at room temperature. The solvent was evaporated and the residue was subjected to flash column chromatography (gradient, 3% MeOH/CH₂Cl₂ to 10% MeOH/CH₂Cl₂) to give 1.09 g (62% yield) of compound **124** as an orange gum.

¹H NMR (CDCl₃) δ 2.01-2.05 (m, 4 H), 2.39 (t, J = 7.9 Hz, 2 H), 3.37-3.43 (m, 4 H), 3.90 (t, J = 7.2 Hz, 2 H), 7.01 (d, J = 5.4 Hz, 1 H), 8.29 (d, J = 5.4 Hz, 1 H), 8.37 (s, 1 H);

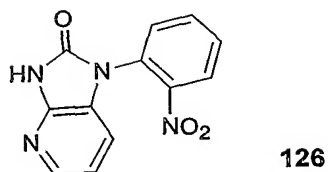
MS m/e 260 (MH⁺).



A mixture of **28A** (1.00 g, 5.71 mmol), *o*-fluoronitrobenzene (0.88 g, 6.28 mmol) and Cs₂CO₃ (5.58 g, 17.1 mmol) in DMF was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc and washed with water and brine, dried over MgSO₄, and concentrated. Purification by flash chromatography (gradient, CH₂Cl₂/hexane, 40:1 to 20:1) gave 1.10 g (65% yield) of **125** as a yellow foam.

¹H NMR (CDCl₃) δ 2.28-2.32 (m, 3 H), 5.45-5.49 (m, 2 H), 7.01-7.05 (m, 1 H), 7.11-7.15 (m, 1 H), 7.62-7.68 (m, 2 H), 7.80-7.84 (m, 1 H), 8.14-8.22 (m, 2 H);

MS m/e 297 (MH⁺).



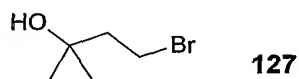
5 Compound **126** was prepared from compound **125** according to the same procedure described for compound **115**.

¹H NMR (DMSO-d₆) δ 7.06-7.09 (m, 1 H), 7.33-7.34 (m, 1 H), 7.75-7.79 (m, 1 H), 7.85-7.87 (m, 1 H), 7.94-7.98 (m, 1 H), 8.04-8.05 (m, 1 H), 8.21-8.23 (m, 1 H);

MS m/e 257 (MH⁺).

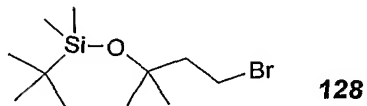
III. Preparation of R₁-LGs:

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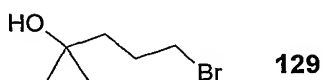
Compound **127** was prepared according to the procedure described by A. Yebga et al. in *Eur. J. Med. Chem.*, **1995**, 30, 769-777.

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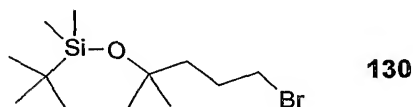
Compound **128** was prepared according to the procedure described by J. C. Heslin and C. J. Moody in *J. Chem. Soc. Perkins Trans. I*, **1988**, 6, 1417-1423.

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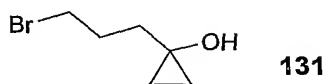
Compound **129** was prepared according to the same procedure described for compound **127**.

¹H NMR (CDCl₃) δ 1.22 (s, 6 H), 1.57-1.60 (m, 2 H), 1.92-1.98 (m, 3 H), 3.42 (t, J = 6.7 Hz, 2 H).



To neat 2,6-lutidine (11.42 g, 106.60 mmol) cooled with an ice bath to 0 °C was added *t*-butyldimethylsilyltrifluoromethane sulfonate (16.91 g, 63.96 mmol). After 30 minutes, a solution of compound **129** (7.72 g, 42.64 mmol) in CH₂Cl₂ (15 mL) was added. The resulting brown reaction mixture was stirred at 0 °C for 2.5 hours. The reaction mixture was poured onto ice (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL) and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and evaporated. The crude brown oil was purified by flash column chromatography (pentane:Et₂O, 15:1) to give compound **130** as a colorless oil.

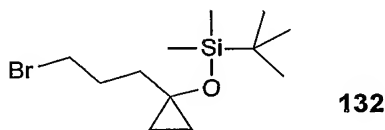
¹H NMR (CDCl₃) δ 0.07 (s, 6 H), 0.85 (s, 9 H), 1.21 (s, 6 H), 1.52-1.55 (m, 2 H), 1.93-1.99 (m, 2 H), 3.42 (t, J = 6.7 Hz, 2 H).



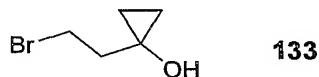
Compound **131** was prepared according to the procedure described by O. Kulinkovich et al. in *Tetrahedron Letters*, **1996**, 37, 1095-1096. To a solution of ethyl-4-bromobutyrate (16.36 g, 83.85 mmol) in Et₂O (200 mL) was added titanium (IV) isopropoxide (2.38 g, 8.39 mmol). Ethylmagnesium bromide (3.0 M in Et₂O, 58.7 mL, 176.09 mmol) was added to the mixture slowly via addition funnel over 30 minutes maintaining the temperature between 10-20 °C. The reaction mixture was stirred for 6 hours at room temperature and then poured

slowly into chilled 10% aqueous H_2SO_4 (300 mL) and stirred. The layers were separated and the aqueous layer was further extracted with Et_2O . The combined organic extracts were dried over MgSO_4 and evaporated. The crude oil was purified by flash column chromatography (gradient, hexanes/ Et_2O 3:1 to 1:1) to give 10.3g (67% yield) of compound **131** as a yellow oil.

^1H NMR (CDCl_3) δ 0.42-0.48 (m, 2 H), 0.69-0.76 (m, 2 H), 1.63-1.70 (m, 2 H), 2.05-2.14 (m, 2 H), 3.45-3.50 (m, 2 H);

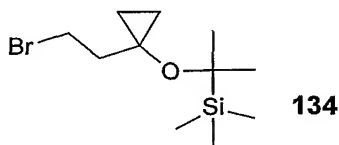


Compound **132** was prepared from compound **131** according to the same procedure described for compound **130** and was used immediately for coupling upon isolation.



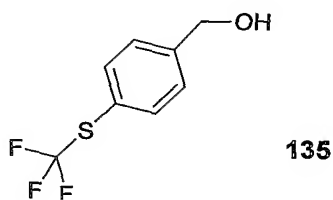
Compound **133** was prepared according to the same procedure described for compound **131** using ethyl 3-bromopropionate.

^1H NMR (CDCl_3) δ 0.51 (t, $J = 6.1$ Hz, 2 H), 0.76 (t, $J = 6.2$ Hz, 2 H), 2.07 (t, $J = 7.3$ Hz, 2 H), 3.57 (t, $J = 7.3$ Hz, 2 H).



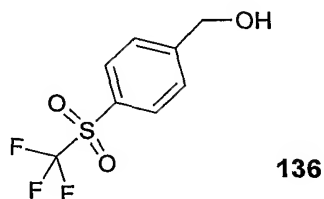
Compound **134** was prepared from compound **133** according to the same procedure described for compound **130**.

^1H NMR (CDCl_3) δ 0.10 (s, 6 H), 0.50 (t, $J = 6.3$ Hz, 2 H), 0.74 (t, $J = 6.3$ Hz, 2 H), 0.85 (s, 9 H), 2.03 (t, $J = 8.0$ Hz, 2 H), 3.56 (t, $J = 8.0$ Hz, 2 H).



A solution of 4-(trifluoromethylthio) benzoic acid (5.00 g, 22.50 mmol) and triethylamine (2.36g, 23.40 mmol) in THF (50 mL) was cooled to 0 °C and to the solution was added ethyl chloroformate (2.53 g, 23.40 mmol). The mixture was filtered and the added dropwise to a cooled solution of sodium borohydride (3.54 g, 93.38 mmol) in a mixture of H_2O and THF (1:1 ratio, 50 mL). The reaction mixture was stirred for 2 hours keeping the temperature below 15 °C and then for 18 hours at room temperature. The reaction was quenched with 1N HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O and all organic layers were combined, dried over Na_2SO_4 , and evaporated. The resulting solid was dissolved in EtOAc and was washed with saturated aqueous NaHCO_3 . The organic layer was dried over Na_2SO_4 and evaporated to give 3.53 g (75% yield) of compound **135** as a white solid.

^1H NMR ($\text{DMSO}-d_6$) δ 4.57 (d, $J = 5.7$ Hz, 2 H), 5.38 (t, $J = 5.7$ Hz, 1 H), 7.48 (d, $J = 7.3$ Hz, 2 H), 7.68 (d, $J = 7.3$ Hz, 1 H).

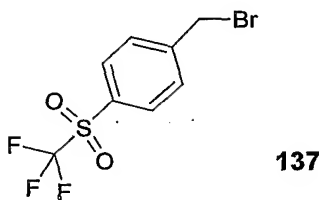


A mixture of compound **135** (3.50 g, 16.81 mmol), hydrogen peroxide (30%, 19.05 g, 168.10 mmol) and glacial acetic acid (40 mL) was stirred at 80 °C

for several minutes and then at 50 °C for 48 hours. The solution was poured into H₂O and extracted with Et₂O. The combined extracts were washed with aqueous 10% NaHCO₃, dried over Na₂SO₂, and evaporated to give 3.6 g (89% yield) of compound **136** as a white solid.

5

¹H NMR (DMSO-d₆) δ 4.70 (d, J = 7.1 Hz, 2 H), 5.61 (bs, 1 H), 7.78 (d, J = 7.2 Hz, 2 H), 8.10 (d, J = 7.2 Hz, 2 H).



10

A solution of alcohol **136** (2.0 g, 8.32 mmol) in Et₂O (50 mL) was cooled to -5 °C with an ice/salt bath. To this solution was added phosphorous tribromide and the resulting mixture was stirred at -5 °C for 5 hours and then at room temperature for 18 hours. The reaction mixture was poured into ice water and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with saturated aqueous NaHCO₃, saturated aqueous NaCl, dried over Na₂SO₄, and evaporated to give 1.45 g (56% yield) of **137** as a clear oil.

15

¹H NMR (DMSO-d₆) δ 4.87 (s, 2 H), 7.91 (d, J = 8.5 Hz, 2 H), 8.15 (d, J = 8.4 Hz, 2 H).

20

IV. Preparation of Examples of Formula I:

Unless a specific procedure is described, Examples 1-166 are prepared according to the general coupling procedures described below:

25

General Coupling Procedure of 2-Chloromethyl-benzimidazoles (II) and 2-Oxo-imidazopyridines or 2-Oxo-imidazopyrimidines in Scheme I-A.

Examples 1-3, 8-12, 14-16, 23-46, 65, 69-70, 72, 90, 94, 102, 104, 111-
5 113, 120, 122, 126, 128-131, 135-136, 140-151, 156-157, 154-155, 157 and 160-
163, and 166 were prepared according to the following procedure:

To a solution of II and 2-oxo-imidazopyridine or 2-oxo-
imidazopyrimidine (1 equivalent of each) in THF or CH₂Cl₂ or DMF is added 3-4
10 equivalents of BTPP or Cs₂CO₃. The mixture is stirred at 0 °C or room
temperature for 1-16 hours. The solvent is evaporated, and the residue is diluted
with water and extracted with EtOAc. The crude product is then purified by
chromatography on silica gel or by reverse phase preparative HPLC.

15 **General Procedure of Reacting Ia with R₂-LG in Scheme I-B.**

Examples 5-7, 18, 100, and 138 were prepared according to the following
procedure:

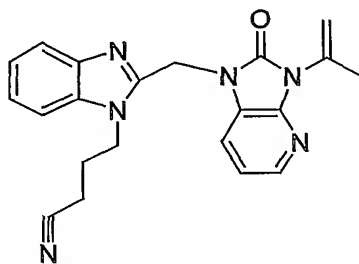
20 To a solution of Ia and 1.5-3 equivalents of BTPP, Cs₂CO₃, or BEMP on
polystyrene resin in THF or DMF is slowly added R₂-LG at room temperature.
When the reaction is completed, the solvent is evaporated or resin is filtered and
filtrate is evaporated. The residue is purified by dissolving in EtOAc or CH₂Cl₂ and
washing with water followed by flash chromatography, or by trituration of the solid
25 collected from the reaction in solvents such as MeOH, or by reverse phase
preparative HPLC.

General Procedure of Reacting V with R₁-LG in Scheme I-C.

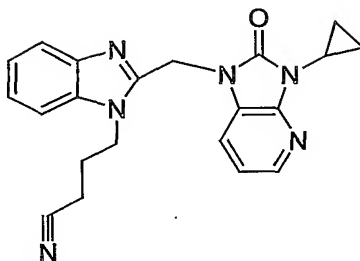
30 Examples 48, 67-68, 76, 78, 80, 82, 84, 88, 124, and 152-153 were
prepared according to the following procedure.

To a mixture of **V** and 1.5-3 equivalents of sodium hydride or BEMP on polystyrene resin in THF, DMF or CH₃CN is added R₁-LG. The reaction is stirred at temperatures ranging from 0 °C to 80 °C for 30 minutes to 18 hours. In examples where BEMP on polystyrene resin is utilized, the resin is filtered. The filtrate is evaporated and the residue is purified by flash column chromatography on silica or reverse phase preparative HPLC. In examples where sodium hydride is used as base, the reaction mixture is diluted with water, extracted with EtOAc or CH₂Cl₂, and purified by flash column chromatography on silica or reverse phase preparative HPLC.

Example 1

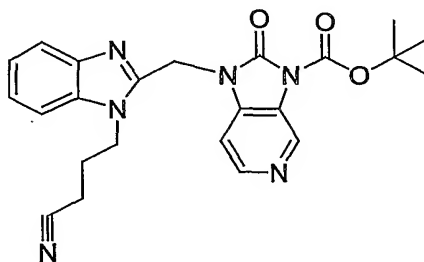


- ¹H NMR (CDCl₃) δ 2.05-2.11 (m, 2 H), 2.29 (s, 3 H), 2.50 (t, J = 7.1 Hz, 2 H), 4.58 (t, J = 7.6 Hz, 2 H), 5.36 (s, 1 H), 5.48 (s, 3 H), 7.06 (dd, J = 5.2, 7.8 Hz, 1 H), 7.35-7.45 (m, 3 H), 7.84 (d, J = 7.4 Hz, 1 H), 7.94 (bd, J = 6.4 Hz, 1 H), 8.08 (dd, J = 1.2, 5.2 Hz, 1 H);
- IR (KBr, cm⁻¹) 3423, 2952, 2243, 1698, 1656, 1618, 1452, 1403, 1336, 1247, 1152, 790, 766, 743;
- MS m/e 373 (MH⁺);
- Anal. Calcd for C₂₁H₂₀N₆O: C, 67.73; H, 5.41; N, 22.57
- Found: C, 67.35; H, 5.35; N, 22.41.

Example 2

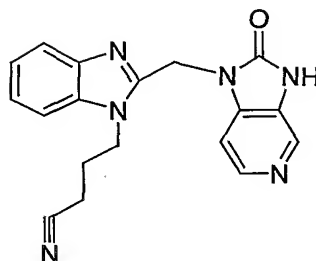
- 5 ^1H NMR (CDCl_3) δ 1.13-1.21 (m, 4 H), 2.06-2.12 (m, 2 H), 2.51 (t, $J = 7.2$ Hz, 2 H), 3.01-3.05 (m, 1 H), 4.57 (t, $J = 7.5$ Hz, 2 H), 5.42 (s, 2 H), 7.01-7.05 (m, 1 H), 7.34-7.47 (m, 3 H), 7.81-7.86 (m, 2 H), 8.10 (d, $J = 4.8$ Hz, 1 H);
IR (KBr, cm^{-1}) 3424, 2244, 1702, 1333, 1474, 1461, 1280, 1164, 789;
MS m/e 373 (MH^+).

10

Example 3

- 15 ^1H NMR (CD_3OD) δ 1.68 (s, 9 H), 2.18-2.21 (m, 2 H), 2.60 (t, $J = 7.2$ Hz, 2 H), 4.50 (t, $J = 7.6$ Hz, 2 H), 5.48 (s, 2 H), 7.23-7.25 (m, 1 H), 7.30 (t, $J = 7.2$ Hz, 1 H), 7.35 (d, $J = 5.4$ Hz, 1 H), 7.54 (d, $J = 8.0$ Hz, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 8.31 (d, $J = 5.4$ Hz, 1 H), 8.88 (s, 1 H);
MS m/e 433 (MH^+).

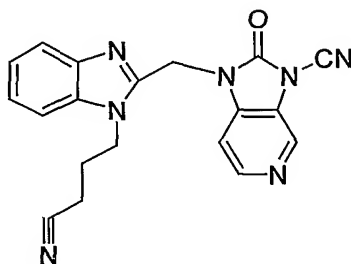
Example 4



5 The *t*-butoxycarbonyl group of Example 4 was removed by treating with aqueous 1 N NaOH solution using the procedure described for the preparation of intermediate compound 43.

¹H NMR (CD₃OD) δ 2.05-2.11 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.39 (s, 2 H), 7.16-7.19 (m, 1 H), 7.24-7.27 (m, 2 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.17 (d, J = 5.2 Hz, 1 H), 8.25 (s, 1 H), 11.34 (s, 1 H); MS m/e 333 (MH⁺).

15 **Example 5**



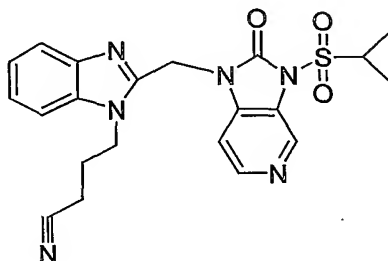
¹H NMR (DMSO-d₆) δ 2.14-2.17 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.52 (s, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 1 H), 7.51 (d, J = 5.3 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 8.47 (d, J = 5.3 Hz, 1 H), 8.65 (s, 1 H);
IR (KBr, cm⁻¹) 3436, 2987, 2263, 1760, 1608, 1384, 1125, 748;
MS m/e 358 (MH⁺);

Anal. Calcd for $C_{19}H_{15}N_7O \cdot 0.6EtOAc$: C, 62.65; H, 4.87; N, 23.90

Found: C, 62.33; H, 4.76; N, 24.14.

Example 6

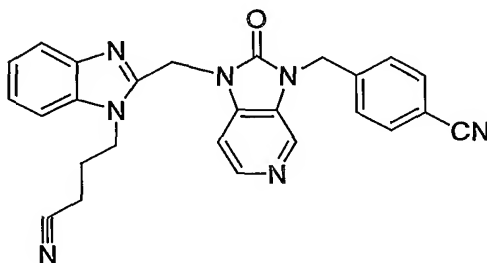
5



1H NMR (CD_3OD) δ 1.53 (d, J = 6.8 Hz, 6 H), 2.27-2.32 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 4.08-4.12 (m, 1 H), 4.57 (t, J = 7.5 Hz, 2 H), 5.68 (s, 2 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.88 (d, J = 6.3 Hz, 2 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.94 (s, 1 H);
IR (KBr, cm^{-1}) 3420, 2314, 2251, 2075, 2008, 1752, 1623, 1509, 1369, 1180, 738;
HRMS m/e 439.1552 (MH^+).

15

Example 7



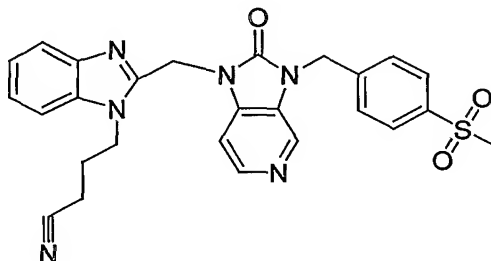
1H NMR ($DMSO-d_6$) δ 2.11-2.12 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.42 (t, J = 7.4 Hz, 2 H), 5.28 (s, 2 H), 5.50 (s, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.26 (t, J = 8.0 Hz, 1 H), 7.35 (d, J = 5.3 Hz, 1 H), 7.55-7.57 (m, 3 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 8.2 Hz), 8.24 (d, J = 5.2 Hz, 1H), 8.40 (s, 1 H);
IR (KBr, cm^{-1}) 3424, 2953, 2250, 2229, 1716, 1609, 1503, 825, 744;
MS m/e 448 (MH^+);

Anal. Calcd for $C_{26}H_{21}N_7O \cdot 0.25H_2O$: C, 69.09; H, 4.79; N, 21.69

Found: C, 69.00; H, 4.81; N, 21.77.

Example 8

5



1H NMR (DMSO- d_6) δ 2.10-2.13 (m, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 3.20 (s, 3 H), 4.43 (t, J = 7.4 Hz, 2 H), 5.30 (s, 2 H), 5.51 (s, 2 H), 7.19 (t, J = 8.0 Hz, 1 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.35 (d, J = 5.2 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.62-7.65 (m, 3 H), 7.93 (d, J = 8.3 Hz, 2 H), 8.24 (d, J = 5.2 Hz, 1 H), 8.43 (s, 1 H);

IR (KBr, cm^{-1}) 3424, 2246, 1707, 1614, 1501, 1407, 1306, 1148;

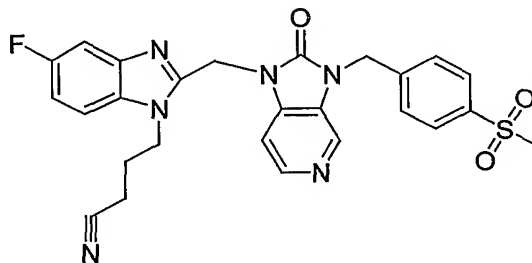
MS m/e 501 (MH^+);

Anal. Calcd for $C_{26}H_{24}N_6O_3S$: C, 62.38; H, 4.83; N, 16.78

Found: C, 62.31; H, 4.73; N, 16.75.

Example 9

20



1H NMR (DMSO- d_6) δ 2.11-2.14 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 3.21 (s, 3 H), 4.44 (t, J = 7.4 Hz, 2 H), 5.30 (s, 2 H), 5.51 (s, 2 H), 7.16 (m, 1 H), 7.36 (d, J = 5.2 Hz, 1 H), 7.40 (q, J = 2.4, 9.7 Hz, 1 H), 7.63-7.68 (m, 3 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.44 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2926, 2248, 1707, 1613, 1602, 1148;

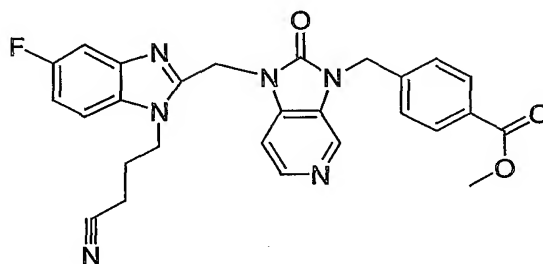
MS m/e 519 (MH^+);

Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{FN}_6\text{O}_3\text{S}$: C, 60.22; H, 4.47, N, 16.20

Found C, 60.06; H, 4.69, N, 16.21.

5

Example 10



10 ^1H NMR (DMSO-d_6) δ 2.09-2.13 (m, 2 H), 2.64 (t, $J = 7.4$ Hz, 2 H), 3.84 (s, 3 H), 4.43 (t, $J = 7.4$ Hz, 2 H), 5.26 (s, 2 H), 5.50 (s, 2 H), 7.13-7.17 (m, 1 H), 7.34-7.40 (m, 2 H), 7.51 (d, $J = 8.3$ Hz, 2 H), 7.64-7.67 (m, 1 H), 7.96-7.97 (m, 2 H), 8.23 (d, $J = 5.2$ Hz, 1 H), 8.39 (s, 1H);

IR (KBr, cm^{-1}) 3432, 2954, 2245, 1719, 1698, 1499, 1284, 1139;

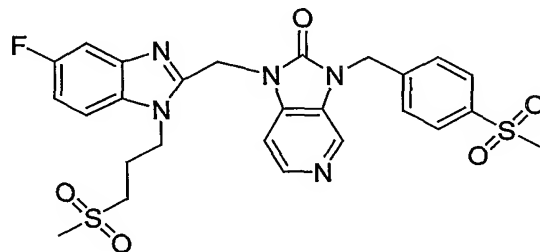
15 MS m/e 499 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{FN}_6\text{O}_3$: C, 65.05; H, 4.65; N, 16.85

Found: C, 65.25; H, 4.65; N, 16.87.

Example 11

20



^1H NMR (DMSO-d_6) δ 2.17-2.23 (m, 2 H), 3.02 (s, 3 H), 3.20 (s, 3H), 3.26 (t, $J = 8.0$ Hz, 2 H), 4.51 (t, $J = 7.7$ Hz, 2 H), 5.29 (s, 2 H), 5.50 (s, 2 H), 7.16 (dt, $J =$

2.4, 9.2 Hz, 1 H), 7.36 (d, $J = 4.9$ Hz, 1 H), 7.40 (dd, $J = 2.4, 9.5$ Hz, 1 H), 7.63 (d, $J = 8.2$ Hz, 2 H), 7.68 (dd, $J = 4.9, 8.9$ Hz, 1 H), 7.93 (d, $J = 8.3$ Hz, 2 H), 8.25 (d, $J = 5.2$ Hz, 1 H), 8.43 (s, 1 H);

IR (KBr, cm^{-1}) 3442, 2925, 2360, 1712, 1614, 1500, 1490, 1296, 1147, 761, 530;

5 MS m/e 572 (MH^+);

Anal. Calcd for $\text{C}_{26}\text{H}_{26}\text{FN}_5\text{O}_5\text{S}_2$:

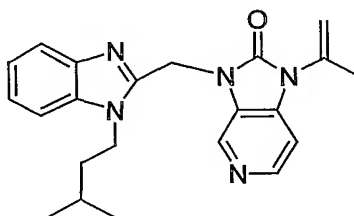
C, 54.62; H, 4.58; N, 12.25

Found:

C, 54.48; H, 4.69; N, 12.14.

Example 12

10



^1H NMR (CDCl_3) δ 0.98 (s, 3 H), 0.95 (s, 3 H), 1.44-1.52 (m, 2 H), 1.60-1.73 (m, 1 H), 2.25 (s, 3 H), 4.28-4.33 (m, 2 H), 5.20 (s, 1 H), 5.41 (s, 3 H), 7.02 (d, $J = 5.1$ hz, 1 H), 7.27-7.31 (m, 3 H), 7.77-7.80 (m, 1 H), 8.31 (d, $J = 5.1$ Hz, 1 H), 8.73 (s, 1 H);

MS m/e 376 (MH^+);

IR (KBr, cm^{-1}) 2957, 1712, 1603, 1494, 1398, 1330, 1167, 1138, 816, 740;

Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}$:

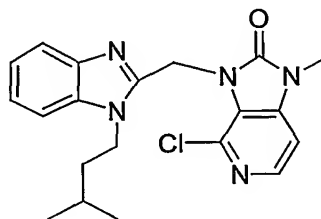
C, 70.38; H, 6.71; N, 18.65

20

Found:

C, 70.24; H, 6.67; N, 18.71.

Example 13



25

To a solution of 4-chloro-1-methyl-1,3-dihydro-imidazo[4,5 c]pyridin-2-one (Salor of Aldrich Chemical, 100 mg, 0.55 mmol) in DMF (10 mL) was added sodium hydride (26 mg, 60% dispersion in mineral oil) at room temperature.

After stirring for 30 min, a neutral form of compound 4 (155 mg, 0.654 mmol)

- 5 was added. The resulting mixture was stirred overnight and evaporated. The residue was diluted with water and extracted with Et₂O. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc, then EtOAc/MeOH, 20:1 to 10:1) to give the Example 13 (78 mg, 38% yield).

10

¹H NMR (CDCl₃) δ 1.07 (d, J = 6.3 Hz, 6 H), 1.72-1.86 (m, 3 H), 3.52 (s, 3 H), 4.27 (t, J = 7.7 Hz, 2 H), 5.64 (s, 2 H), 6.98 (d, J = 5.3 Hz, 1 H), 7.18-7.30 (m, 2 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.66 (d, J = 7.4 Hz, 1 H), 8.13 (d, J = 5.3 Hz, 1 H); IR (KBr, cm⁻¹) 3449, 2954, 1735, 1613, 1586, 1503, 1441, 1133, 775;

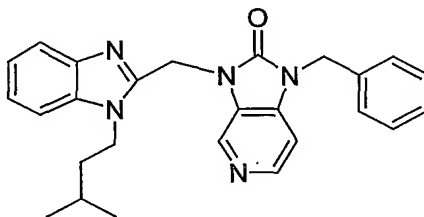
- 15 MS m/e 384 (MH⁺);

Anal. Calcd for C₂₀H₂₂ClN₅O • 1.10 H₂O: C, 59.50; H, 6.04; N, 17.35

Found: C, 59.46; H, 5.47; N, 16.68

Example 14

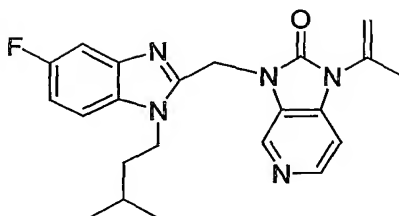
20



¹H NMR (CDCl₃) δ 1.07 (d, J = 6.1 Hz, 6 H), 1.78-1.84 (m, 3 H), 4.42 (bt, J = 8.0 Hz, 2 H), 5.21 (s, 2 H), 5.77 (s, 2 H), 7.14 (d, J = 6.2 Hz, 1 H), 7.33-7.49 (m, 8 H), 7.94 (d, J = 8.0 Hz, 1 H), 8.34 (d, J = 6.3 Hz, 1 H), 9.00 (s, 1 H);

25

MS m/e 376 (MH⁺).

Example 15

5 ^1H NMR (CD_3OD) δ 0.97 (d, $J = 6.3$ Hz, 6 H), 1.44-1.49 (m, 2 H), 1.62-1.73 (m, 1 H), 2.25 (s, 3 H), 4.27-4.33 (m, 2 H), 5.21 (s, 1 H), 5.38 (s, 2 H), 5.42 (s, 1 H), 7.02-7.08 (m, 2 H), 7.23 (dd, $J = 4.5, 9.0$ Hz, 1 H), 7.45 (dd, $J = 2.4, 9.3$ Hz, 1 H), 8.33 (d, $J = 5.1$ Hz, 1 H), 8.17 (s, 1 H);

IR (KBr, cm^{-1}) 2960, 1713, 1605, 1495, 1455, 1399, 1333, 1163, 1140, 848, 813;

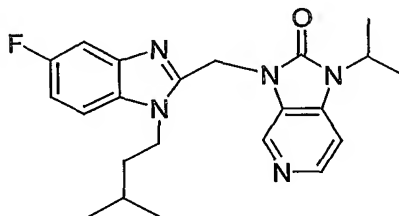
10 MS m/e 394 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{FN}_5\text{O}$: C, 67.16; H, 6.15; N, 17.80

Found: C, 67.25; H, 5.96; N, 17.88.

Example 16

15



^1H NMR (CDCl_3) δ 0.97 (d, $J = 6.9$ Hz, 6 H), 1.43-1.50 (m, 2 H), 1.55 (d, $J = 7.2$ Hz, 6 H), 1.55-1.75 (m, 1 H), 4.26-4.31 (m, 2 H), 4.70-4.80 (m, 1 H), 5.37 (s, 2 H), 7.01-7.08 (m, 2 H), 7.22 (dd, $J = 4.8, 8.9$ Hz, 1 H), 7.44 (dd, $J = 2.7, 9.3$ Hz, 1 H), 8.29 (d, $J = 5.4$ Hz, 1 H), 8.68 (s, 1 H);

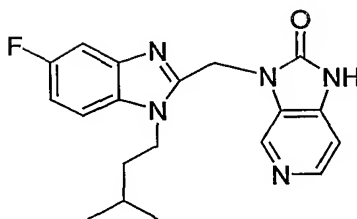
IR (KBr, cm^{-1}) 2956, 1706, 1493, 1456, 1389, 1332, 1133, 1113, 847;

MS m/e 396 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{FN}_5\text{O} \cdot 0.33\text{H}_2\text{O}$: C, 65.82; H, 6.69; N, 17.44

25

Found: C, 65.83; H, 6.30; N, 17.43.

Example 17

- 5 A solution of Example 15 (4.0 g, 10.17 mmol) in a mixture of MeOH (10 mL) and 6 N HCl (20 mL) was stirred at reflux overnight. The solution was cooled to room temperature and neutralized with concentrated NaOH solution, and evaporated. The residue was taken up with CH₂Cl₂, dried over MgSO₄, and evaporated. The residue was triturated with hot EtOAc and filtered to give
- 10 Example 17 (3.22 g, 90% yield) as a white solid.

¹H NMR (CDCl₃) δ 0.99 (d, J = 6.6 Hz, 6 H), 1.50-1.55 (m, 2 H), 1.71-1.77 (m, 1 H), 4.25-4.31 (m, 2 H), 5.36 (s, 2 H), 6.97 (d, J = 5.1 Hz, 1 H), 7.06 (dt, J = 2.4, 9.3 Hz, 1 H), 7.23 (dd, J = 4.5, 8.7 Hz, 1 H), 7.43 (dd, J = 2.4, 9.3 Hz, 1 H), 8.29

15 (d, J = 5.1 Hz, 1 H), 8.62 (s, 1 H), 9.89 (bs, 1 H);

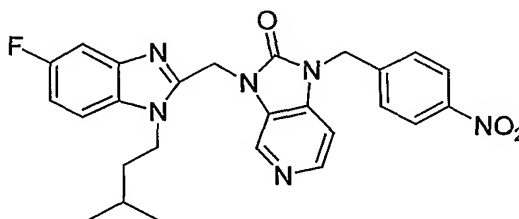
IR (KBr, cm⁻¹) 2958, 1720, 1622, 1491, 1455, 1139, 1014, 958, 894, 813;

MS m/e 375 (MH⁺);

Anal. Calcd for C₁₉H₂₀FN₅O: C, 64.58; H, 5.70; N, 19.82

Found: C, 64.26; H, 5.58; N, 19.85.

20

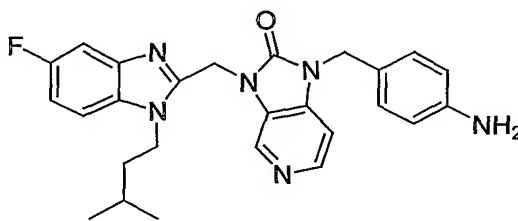
Example 18

¹H NMR (CDCl₃) δ 0.99 (d, J = 6.7 Hz, 6 H), 1.54-1.59 (m, 2 H), 1.69-1.73 (m, 1 H), 4.29 (t, J = 9.2 Hz, 2 H), 5.20 (s, 2 H), 5.43 (s, 2 H), 6.86 (d, J = 5.4 Hz, 1 H), 7.05 (dt, J = 2.4, 9.1 Hz, 1 H), 7.24 (dd, J = 4.5, 8.9 Hz, 1 H), 7.41 (dd, J = 2.4, 9.3 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 2 H), 8.21 (d, J = 8.7 Hz, 2 H), 8.29 (d, J = 5.2 Hz, 1 H), 8.76 (s, 1 H);
IR (KBr, cm⁻¹) 3424, 2959, 1716, 1611, 1524, 1492, 1346, 1176, 1137, 800;
MS m/e 489 (MH⁺).

Anal. Calcd for C₂₆H₂₅FN₃O₃: C, 63.92; H, 5.16; N, 17.20

Found: C, 63.95; H, 5.13; N, 17.22.

Example 19



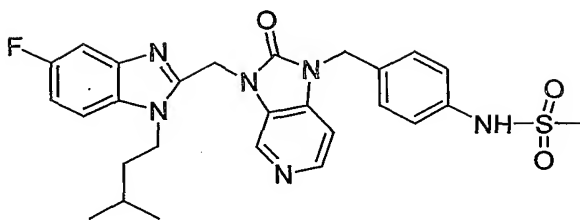
A mixture of Example 18 (1.52 g, 3.11 mmol) and 10% palladium on carbon (150 mg) in MeOH (50 mL) and concentrated hydrochloric acid (1 mL) was agitated under hydrogen at 55 psi for 1.5 hours. The reaction mixture was filtered through a pad of Celite, rinsing thoroughly with MeOH. The filtrate was evaporated and dried under vacuum to give Example 19 as an HCl salt (1.82 g, quantitative yield).

¹H NMR (CD₃OD) δ 1.09 (d, J = 6.0 Hz, 6 H), 1.84-1.90 (m, 3 H), 4.64 (t, J = 7.6 Hz, 2 H), 5.40 (s, 2 H), 5.94 (s, 2 H), 7.43-7.47 (m, 3 H), 7.52 (dd, J = 2.3, 8.1 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 6.5 Hz, 1 H), 7.93 (dd, J = 4.2, 9.1 Hz, 1 H), 8.59 (d, J = 6.4 Hz, 1 H), 9.01 (s, 1 H);
IR (KBr, cm⁻¹) 3411, 2869, 1748, 1655, 1621, 1517, 1496, 1130, 810;
MS m/e 459 (MH⁺);

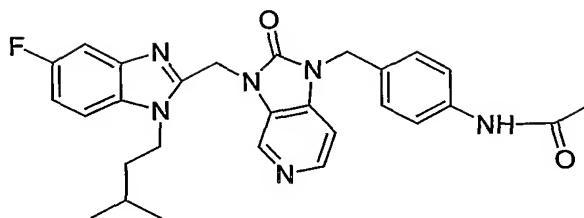
Anal. Calcd for C₂₆H₂₇FN₆O₃•3HCl•2.5H₂O: C, 50.95; H, 5.76; N, 13.71

Found: C, 50.72; H, 5.47; N, 13.66.

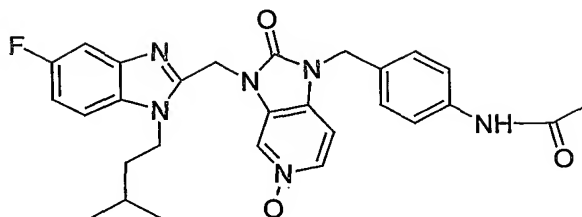
Example 20



- 5 To a mixture of Example 19 (350 mg, 0.66 mmol) and triethylamine (200 mg, 1.98 mmol) in CH₂Cl₂ cooled to 0 °C was added methanesulfonyl chloride (75 mg, 0.66 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 16 hours. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with saturated aqueous sodium bicarbonate solution
- 10 (10 mL) and brine solution (10 mL). The aqueous layer was back-extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, and evaporated. Trituration of the resulting pale yellow solid with Et₂O gave the title compound (quantitative yield).
- 15 ¹H NMR (CD₃OD) δ 1.06 (d, J = 6.3 Hz, 6 H), 1.75-1.81 (m, 3 H), 2.93 (s, 3 H), 4.46 (t, J = 8.2 Hz, 2 H), 5.28 (s, 2 H), 5.64 (s, 2 H), 7.18 (t, J = 2.5, 9.2 Hz, 1 H), 7.23-7.29 (m, 3 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.60 (dd, J = 4.4, 8.9 Hz, 1 H), 7.77 (d, J = 6.5 Hz, 1 H), 8.48 (d, J = 6.7 Hz, 1 H), 8.78 (s, 1 H);
- IR (KBr, cm⁻¹) 3441, 2959, 1736, 1617, 1515, 1332, 1150, 1040, 821;
- 20 MS m/e 537 (MH⁺);
- Anal. Calcd for C₂₇H₂₉FN₆O₃S•4.5H₂O: C, 52.50; H, 6.20; N, 13.61
- Found: C, 52.20; H, 5.79; N, 12.79.

Example 21

- 5 To a mixture of Example 19 (400 mg, 0.75 mmol) and triethylamine (229 mg, 2.26 mmol) in CH₂Cl₂ cooled to 0 °C was added acetyl chloride (74 mg, 0.94 mmol) followed by a catalytic amount of dimethylaminopyridine (10 mg). The reaction was allowed to warm to room temperature and a pale yellow precipitate came out of solution. After 1 hour, the reaction mixture was diluted with CH₂Cl₂
- 10 and washed with saturated aqueous sodium bicarbonate solution and brine. The aqueous layer was back-extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, and evaporated. Trituration of the resulting white solid with Et₂O gave Example 21 (321 mg, 85% yield).
- 15 ¹H NMR (CD₃OD) δ 0.96 (d, J = 0.96 Hz, 6 H), 1.54-1.59 (m, 2 H), 1.67-1.70 (m, 1 H), 2.10 (s, 3 H), 4.36 (t, J = 8.2 Hz, 2 H), 5.13 (s, 2 H), 5.51 (s, 2 H), 7.11 (dt, J = 2.5, 9.2 Hz, 1 H), 7.21 (d, J = 5.4 Hz, 1 H), 7.30 (dd, J = 2.4, 9.3 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 2 H), 7.49 (dd, J = 4.5, 9.0 Hz, 1 H), 7.54 (d, J = 8.6 Hz, 2 H), 8.19 (d, J = 5.4 Hz, 1 H), 8.35 (s, 1 H);
- 20 IR (KBr, cm⁻¹) 3424, 2960, 1724, 1691, 1610, 1517, 1507, 1455, 1402, 1319, 1136, 810;
- MS m/e 501 (MH⁺);
- Anal. Calcd for C₂₈H₂₉FN₆O₂•0.5H₂O: C, 66.00; H, 5.93; N, 16.49
- Found: C, 65.79; H, 6.12; N, 16.29.

Example 22

5 To a solution of the Example 20 (50 mg, 0.10 mmol) in DMF (5 mL) was added *m*-chloroperbenzoic acid (34 mg, 0.20 mmol). The mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure. The resulting residue was triturated with water and filtered. The aqueous filtrate was extracted with EtOAc and the combined extracts were dried
10 over MgSO₄, and evaporated. The residue combined with the solid obtained from trituration were subjected to flash chromatography (gradient, CH₂Cl₂/5% ammonium hydroxide in MeOH, 40:1 to 20:1) to give Example 22 as a white solid (21 mg, 41% yield).

15 ¹H NMR (DMSO-d₆) δ 0.95 (d, J = 6.5 Hz, 6 H), 1.57-1.60 (m, 2 H), 1.66-1.74 (m, 1 H), 2.02 (s, 3 H), 4.32 (t, J = 7.7 Hz, 2 H), 5.05 (s, 2 H), 5.41 (s, 2 H), 7.13 (t, J = 8.7 Hz, 1 H), 7.24 (d, J = 6.7 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 1 H), 7.41 (d, J = 8.6 Hz, 1 H), 7.54 (d, J = 8.2 Hz, 1 H), 7.55-7.59 (m, 1 H), 7.96 (d, J = 6.3 Hz, 1 H), 8.37 (s, 1 H);

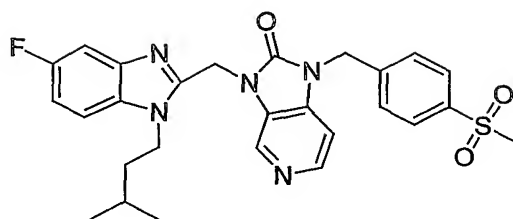
20 IR (KBr, cm⁻¹) 3428, 2956, 1720, 1678, 1600, 1551, 1514, 1465, 1407, 1320, 1162, 1146, 802;

MS m/e 517 (MH⁺);

Anal. Calcd for C₂₈H₂₉FN₆O₃•0.5H₂O: C, 63.99; H, 5.75; N, 15.99

Found: C, 64.08; H, 5.57; N, 15.82.

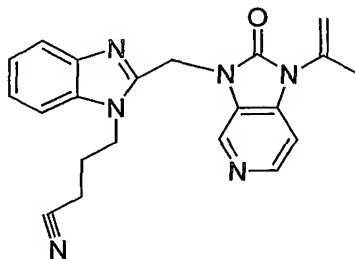
Example 23



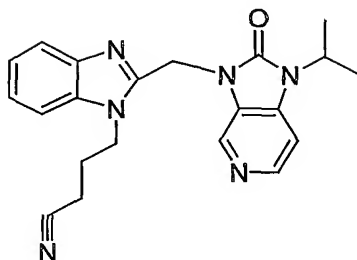
- 5 ^1H NMR (CD_3OD) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.59-1.64 (m, 2 H), 1.69-1.73 (m, 1 H), 3.09 (s, 3 H), 4.39 (t, J = 8.1 Hz, 2 H), 5.31 (s, 2 H), 5.52 (s, 2 H), 7.12 (dt, J = 2.5, 9.2 Hz, 1 H), 7.23 (d, J = 5.4 Hz, 1 H), 7.29 (dd, J = 2.4, 9.2 Hz, 1 H), 7.51 (dd, J = 4.5, 8.9 Hz, 1 H), 7.66 (d, J = 8.4 Hz, 2 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.22 (d, J = 1.7 Hz, 1 H), 8.39 (s, 1 H);
- 10 IR (KBr, cm^{-1}) 3423, 2959, 1715, 1613, 1602, 1497, 1454, 1407, 1307, 1148, 1090, 808, 520;
- MS m/e 522 (MH^+).

Example 24

15



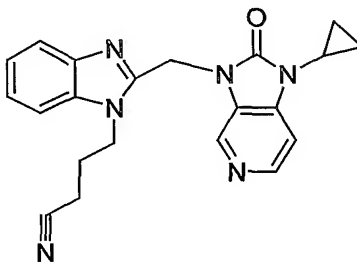
- ^1H NMR (CD_3OD) δ 1.85-1.90 (m, 2 H), 1.90 (s, 3 H), 2.27 (t, J = 7.5 Hz, 2 H), 4.29-4.34 (t, J = 7.5 Hz, 2 H), 5.03 (s, 1 H), 5.65 (s, 1 H), 6.86 (d, J = 5.5 Hz, 1 H), 7.12-7.22 (m, 3 H), 7.60-7.63 (m, 1 H), 8.16 (d, J = 5.5 Hz, 1 H), 8.65 (s, 1 H);
- 20 IR (KBr, cm^{-1}) 3396, 2244, 1710, 1660, 1604, 1493, 1458, 1399, 1332, 1166, 1140, 824, 742;
- MS m/e 373 (MH^+);
- Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O} \cdot 0.25 \text{H}_2\text{O}$: C, 66.92; H, 5.48; N, 22.30
- 25 Found: C, 66.58; H, 5.56; N, 22.34.

Example 25

5

^1H NMR (CDCl_3) δ 1.56 (d, $J = 6.9$ Hz, 6 H), 1.98-2.08 (m, 2 H), 2.45 (t, $J = 7.2$ Hz, 2 H), 4.49 (t, $J = 7.2$ Hz, 2 H), 4.70-4.74 (m, 1 H), 5.40 (s, 2 H), 7.06 (d, $J = 5.2$ Hz, 1 H), 7.33-7.39 (m, 3 H), 7.78-7.81 (m, 1 H), 8.31 (d, $J = 5.2$ Hz, 1 H), 8.81 (s, 1 H);

10 IR (KBr, cm^{-1}) 3412, 2981, 2246, 1700, 1608, 1496, 1459, 1391, 1117, 748;
MS m/e 375 (MH^+).

Example 26

15

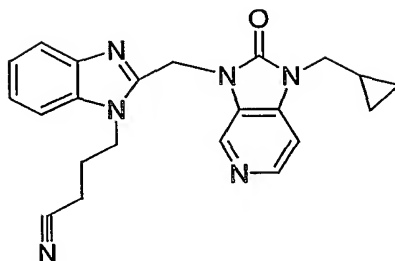
^1H NMR (CDCl_3) δ 1.03-1.06 (m, 2 H), 1.97-1.24 (m, 2 H), 2.13-2.18 (m, 2 H), 2.47 (t, $J = 4.2$ Hz, 2 H), 2.96-3.00 (m, 1 H), 4.51 (t, $J = 4.4$ Hz, 2 H), 4.16 (s, 2 H), 7.27-7.35 (m, 4 H), 7.38 (dd, $J = 0.8, 4.2$ Hz, 1 H), 7.77 (dd, $J = 0.9, 4.4$ Hz, 1 H), 8.37 (d, $J = 3.4$ Hz, 1 H), 8.56 (s, 1 H);

20

IR (KBr, cm^{-1}) 3405, 2245, 1702, 1608, 1500, 1408, 1172, 1024, 820, 743;
MS m/e 373 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_8\text{O} \cdot 0.875\text{H}_2\text{O}$: C, 64.98; H, 5.64; N, 21.65

Found: C, 65.06; H, 5.36; N, 21.51.

Example 27

5

^1H NMR (CD_3OD) δ 0.53-0.54 (m, 2 H), 0.64-0.66 (m, 2 H), 1.31-1.37 (m, 1 H), 2.30-2.34 (m, 2 H), 2.68 (t, $J = 7.2$ Hz, 2 H), 4.02 (d, $J = 7.2$ Hz, 2 H), 4.63 (t, $J = 7.4$ Hz, 2 H), 5.72 (s, 2 H), 7.39 (t, $J = 7.0$ Hz, 1 H), 7.43 (t, $J = 7.1$ Hz, 1 H), 7.63 (d, $J = 7.9$ Hz, 1 H), 7.73 (d, $J = 8.1$ Hz, 2 H), 7.92 (d, $J = 6.5$ Hz, 1 H), 8.55 (d, $J = 6.5$ Hz, 1 H), 8.81 (s, 1 H);

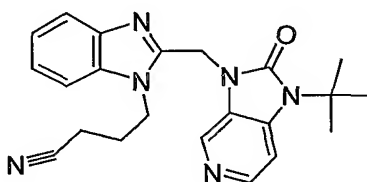
10

IR (KBr, cm^{-1}) 3448, 2250, 1748, 1676, 1522, 1201, 1131, 720;

MS m/e 387 (MH^+).

Example 28

15

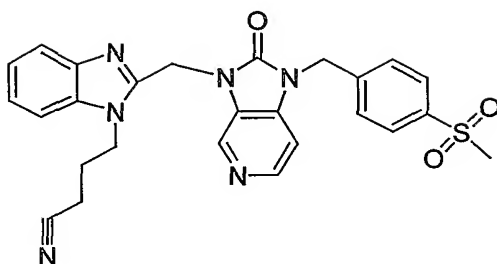


^1H NMR (CDCl_3) δ 1.81 (s, 9 H), 2.05-2.06 (m, 2 H), 2.46 (t, $J = 7.2$ Hz, 2 H), 4.48 (t, $J = 7.6$ Hz, 2 H), 5.38 (s, 2 H), 7.31-7.36 (m, 4 H), 7.78 (m, 1 H), 8.24 (d, $J = 5.8$ Hz, 1 H), 8.84 (s, 1 H);

20

IR (KBr, cm^{-1}) 3406, 2937, 2246, 1706, 1493, 1458, 1387, 1157, 1138, 746;

MS m/e 389 (MH^+).

Example 29

5 ^1H NMR (DMSO-d_6) δ 2.09-2.12(m, 2 H), 2.63 (t, $J = 7.4$ Hz, 2 H), 4.43 (t, $J = 7.5$ Hz, 2 H), 5.28 (s, 2 H), 5.52 (s, 2 H), 7.21 (t, $J = 7.2$ Hz, 1 H), 7.26 (t, $J = 7.2$ Hz, 1 H), 7.57 (d, $J = 8.0$ Hz, 1 H), 7.60-7.63 (m, 4 H), 7.92 (d, $J = 8.4$ Hz, 2 H), 8.23 (d, $J = 5.3$ Hz, 1 H), 8.50 (s, 1 H);

IR (KBr, cm^{-1}) 3426, 2246, 1716, 1407, 1150, 760;

10 MS m/e 501 (MH^+);

Anal. Calcd for $\text{C}_{27}\text{H}_{28}\text{FN}_5\text{O}_3\text{S}$:

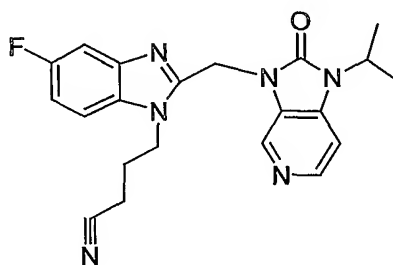
C, 62.17; H, 5.17; N, 13.43

Found:

C, 62.03; H, 5.45; N, 13.34.

Example 30

15



20 ^1H NMR (CDCl_3) δ 1.54 (d, $J = 7.0$ Hz, 6 H), 1.99-2.05 (m, 2 H), 2.45 (t, $J = 7.2$ Hz, 2 H), 4.47 (t, $J = 7.6$ Hz, 2 H), 4.70 (m, 1H), 5.36 (s, 2 H), 7.06-7.10 (m, 2 H), 7.27-7.30 (m, 1 H), 7.45 (q, $J = 2.4, 9.1$ Hz, 1 H), 8.31 (d, $J = 4.0$ Hz, 1 H), 8.78 (s, 1 H);

IR (KBr, cm^{-1}) 3432, 2953, 2360, 2245, 1718, 1698, 1284, 1139;

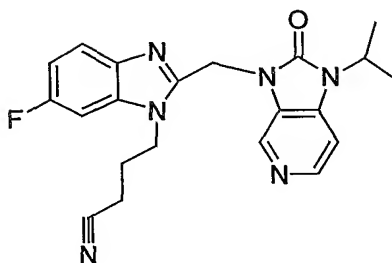
MS m/e 393 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{FN}_6\text{O}$:

C, 64.27; H, 5.39; N, 21.41

Found: C, 64.23, H, 5.44; N, 21.24.

Example 31



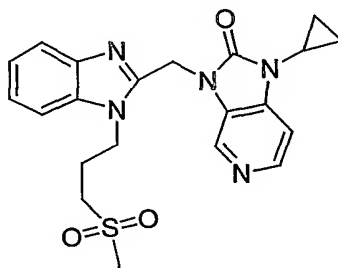
5

^1H NMR (CDCl_3) δ 1.53 (d, $J = 7.0$ Hz, 6 H), 1.96-2.03 (m, 2 H), 2.45 (t, $J = 7.2$ Hz, 2 H), 4.41 (t, $J = 7.6$ Hz, 2 H), 4.70 (m, 1 H), 5.34 (s, 2 H), 6.99-7.06 (m, 3 H), 7.67-7.70 (m, 1 H), 8.29 (d, $J = 4.0$ Hz, 1H), 8.76 (s, 1 H);

10 IR (KBr, cm^{-1}) 3423, 2941, 2247, 1710, 1492, 1390, 808;

MS m/e 393 (MH^+).

Example 32



15

^1H NMR (CDCl_3) δ 1.03-1.06 (m, 2 H), 1.17-1.22 (m, 2H), 2.25-2.31 (m, 2 H), 2.93 (s, 3 H), 2.98-3.01 (m, 1 H), 3.10 (t, $J = 7.4$ Hz, 2 H), 4.54 (t, $J = 7.5$ Hz, 2 H), 5.42 (s, 2 H), 7.25-7.39 (m, 4 H), 7.76 (d, $J = 7.1$ Hz, 1 H), 8.36 (d, $J = 5.3$ Hz, 1 H), 8.79 (s, 1 H);

20

IR (KBr, cm^{-1}) 3423, 2927, 1718, 1608, 1499, 1459, 1409, 1311, 1289, 1128, 748;

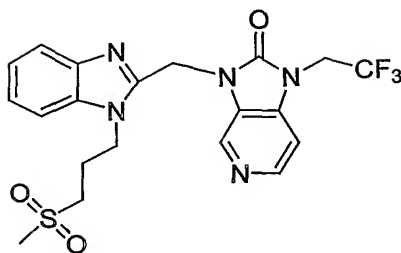
MS m/e 426(MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$:

C, 59.27; H, 5.44; N, 16.45

Found:

C, 59.03; H, 5.52; N, 16.31.

Example 33

5 ^1H NMR ($\text{DMSO}-d_6$) δ 2.13-2.20 (m, 2 H), 3.01 (s, 3 H), 3.26 (t, $J = 7.8$ Hz, 2 H), 4.50 (t, $J = 7.5$ Hz, 2 H), 4.91 (q, $J = 9.3$ Hz, 2 H), 5.53 (s, 2 H), 7.20 (t, $J = 7.3$ Hz, 1 H), 7.28 (t, $J = 7.7$ Hz, 1 H), 7.45 (d, $J = 5.3$ Hz, 1 H), 7.64 (d, $J = 8.1$ Hz, 1 H) 8.32 (d, $J = 5.3$ Hz, 1 H), 8.52 (s, 1 H);

IR (KBr, cm^{-1}) 3441, 1725, 1498, 1460, 1408, 1294, 1265, 1167, 1125, 746;

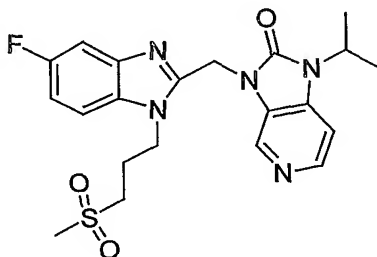
10 MS m/e 468 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_5\text{O}_3\text{S} \cdot 0.375 \text{H}_2\text{O}$: C, 50.66; H, 4.41; N, 14.76

Found: C, 50.83; H, 4.34; N, 14.41.

Example 34

15



20 ^1H NMR (CD_3OD) δ 1.47 (d, $J = 6.9$ Hz, 6 H), 2.14-2.17 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.8$ Hz, 2 H), 4.50 (d, $J = 7.5$ Hz, 2 H), 4.63-4.66 (m, 1 H), 5.44 (s, 2 H), 7.16 (dt, $J = 2.5, 9.2$ Hz, 1 H), 7.41-7.45 (m, 2 H), 7.67 (dd, $J = 4.8, 8.9$ Hz, 1 H), 8.23 (d, $J = 5.4$ Hz, 1 H), 8.47 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2984, 2937, 1702, 1608, 1495, 1457, 1391, 1293, 1135, 1116, 963, 809;

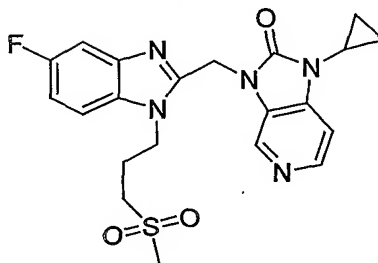
MS m/e 446 (MH^+);

Anal. Calcd for $C_{21}H_{24}FN_5O_3S$:

C, 56.61; H, 5.43; N, 15.71

Found:

C, 56.46; H, 5.55; N, 15.62.

Example 35

5

1H NMR (CD_3OD) δ 0.91-0.93 (m, 2 H), 1.06-1.07 (m, 2 H), 2.99-3.01 (m, 1 H), 3.00 (s, 3 H), 3.23 (t, $J = 7.7$ Hz, 2 H), 4.49 (t, $J = 7.5$ Hz, 2 H), 5.41 (s, $J = 2$ H), 7.15 (dt, $J =$, 1 H), 7.29 (dd, $J = 2.0, 5.3$ Hz, 1 H), 7.43 (dd, $J = 2.5, 9.8$ Hz, 1 H), 7.67 (dd, $J = 4.7, 8.9$ Hz, 1 H), 8.26 (d, $J = 5.3$ Hz, 1 H), 8.44 (s, 1 H);

10 IR (KBr, cm^{-1}) 3423, 3014, 1708, 1609, 1498, 1455, 1415, 1315, 1294, 1171, 1131, 957, 819;

MS m/e 444 (MH^+);Anal. Calcd for $C_{21}H_{22}FN_5O_3S$:

C, 56.87; H, 5.00; N, 15.79

Found:

C, 56.76; H, 5.15; N, 15.69.

15

Example 35 was converted to an oxalate salt by adding 1 equivalent of oxalic acid to a MeOH solution of 35 and evaporating the solvent.

1H NMR (CD_3OD) δ 2.26 (s, 3 H), 2.26-2.36 (m, 2 H), 2.64 (t, $J = 7.5$ Hz, 2 H), 4.62 (t, $J = 7.5$ Hz, 2 H), 5.29 (s, 1 H), 5.45 (s, 1 H), 5.58 (s, 2 H), 7.16 (dd, $J = 5.4, 8.1$ Hz, 1 H), 7.34-7.44 (m, 2 H), 7.54-7.71 (m, 2 H), 7.70 (d, $J = 8.1$ Hz, 1 H), 8.01 (dd, $J = 0.9, 5.4$ Hz, 1 H);

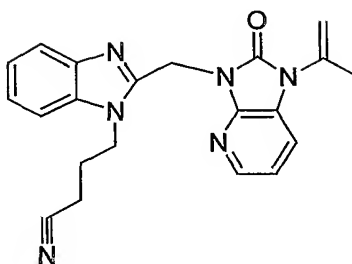
20 IR (KBr, cm^{-1}) 3405, 2954, 2244, 1702, 1611, 1476, 1456, 1400, 1276, 1188, 1158, 795, 749;

25 MS m/e 373 (MH^+);Anal. Calcd for $C_{21}H_{20}N_6O \cdot C_2H_2O_4 \cdot 0.25H_2O$:

C, 59.16; H, 4.86; N, 18.00

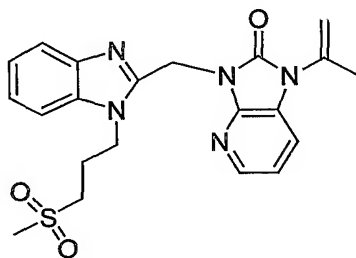
Found:

C, 58.90; H, 4.83; N, 18.24.

Example 36

- 5 ^1H NMR (CDCl_3) δ 2.19-2.45 (m, 2 H), 2.45 (s, 3 H), 2.48 (t, $J = 7.1$ Hz, 2 H), 4.61 (t, $J = 7.4$ Hz, 2 H), 5.19 (s, 1 H), 5.34 (s, 1H), 5.48 (s, 2 H), 7.03 (dd, $J = 5.2, 7.9$ Hz, 1 H), 7.26-7.33 (m, 3 H), 7.80 (d, $J = 8.0$ Hz, 1 H), 8.10 (dd, $J = 1.4, 5.2$ Hz, 1 H).

10

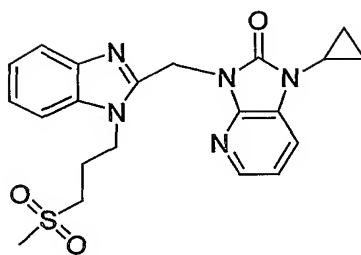
Example 37

- 15 ^1H NMR (CDCl_3) δ 2.28-2.34 (s over m, 5 H), 2.94 (s, 3 H), 3.16 (t, $J = 7.2$ Hz, 2 H), 4.59 (t, $J = 7.9$ Hz, 2 H), 5.37 (s, 1 H), 5.47 (s, 1 H), 5.54 (s, 2 H), 7.08 (dd, $J = 5.3, 7.8$ Hz, 1 H), 7.39-7.43 (m, 2 H), 7.51 (d, $J = 7.7$ Hz, 1 H), 7.85 (d, $J = 7.3$ Hz, 1 H), 8.05 (bs, 1 H), 8.09 (dd, $J = 1.0, 5.2$ Hz, 1 H);

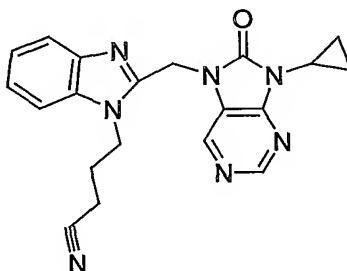
IR (KBr, cm^{-1}) 3423, 1708, 1618, 1453, 1402, 1295, 1131, 750;

MS m/e 426 (MH^+);

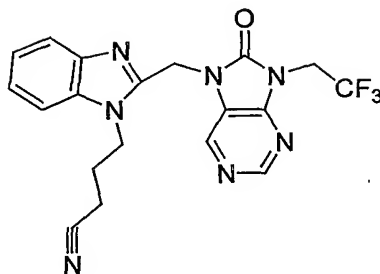
- 20 Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$: C, 59.28; H, 5.44; N, 16.45
 Found: C, 59.11; H, 5.36; N, 16.35.

Example 38

- 5 ^1H NMR (CDCl_3) δ 1.06-1.11 (m, 4 H), 2.49-2.54 (m, 2 H), 2.94-2.99 (m, 1 H), 3.24 (t, $J = 6.7$ Hz, 2 H), 4.75 (t, $J = 7.1$ Hz, 2 H), 5.70 (s, 2 H), 7.05 (dd, $J = 5.3$, 7.7 Hz, 1 H), 7.37-7.44 (m, 3 H), 7.54 (d, $J = 8.0$ Hz, 1 H), 7.91 (d, $J = 8.0$ Hz, 1 H), 7.98 (d, $J = 4.8$ Hz, 1 H);
IR (KBr, cm^{-1}) 3435, 1716, 1617, 1486, 1460, 1425, 1295, 1131, 747;
10 MS m/e 426 (MH^+).

Example 39

- 15 ^1H NMR ($\text{DMSO}-d_6$) δ 1.02-1.07 (m, 4 H), 2.08-2.14 (m, 2 H), 2.64 (t, $J = 7.4$ Hz, 2 H), 3.02-3.03 (m, 1 H), 4.42 (t, $J = 7.4$ Hz, 2 H), 5.44 (s, 1 H), 7.19 (t, $J = 7.5$ Hz, 1 H), 7.28 (t, $J = 7.2$ Hz, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 8.46 (s, 1 H), 8.66 (s, 1 H);
20 IR (KBr, cm^{-1}) 3452, 2244, 1731, 1718, 1612, 1488, 1422, 1407, 1317, 746;
MS m/e 374 (MH^+);
Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_7\text{O}$: C, 64.33; H, 5.12; N, 26.25
Found: C, 64.00; H, 5.20; N, 26.12.

Example 40

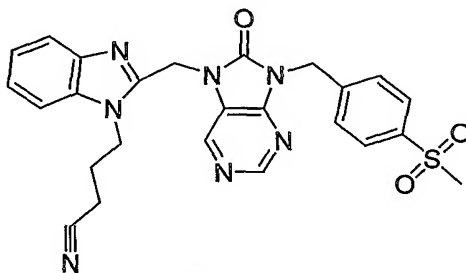
¹H NMR (CDCl₃) δ 2.07-2.13 (m, 2 H), 2.48 (t, J = 6.9 Hz, 2 H), 4.52 (d, J = 7.6 Hz, 2 H), 4.59-4.64 (m, 2 H), 5.47 (s, 2 H), 7.33-7.44 (m, 3 H), 7.80 (d, J = 7.5 Hz, 1 H), 8.76 (s, 1 H), 8.88 (s, 1 H);

MS m/e 416 (MH⁺);

Anal. Calcd for C₁₉H₁₆F₃N₇O: C, 54.94; H, 3.88; N, 23.60

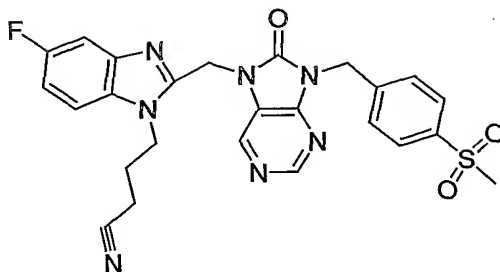
Found: C, 54.87; H, 3.78; N, 23.66.

10

Example 41

15 ¹H NMR (CDCl₃) δ 2.12-2.15 (m, 2 H), 2.43 (t, J = 7.0 Hz, 2 H), 3.02 (s, 3 H), 4.51 (t, J = 7.4 Hz, 2 H), 5.22 (s, 2 H), 5.45 (s, 2 H), 7.32-7.42 (m, 3 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.77-7.79 (m, 1 H), 7.91-7.93 (m, 2 H), 8.73 (s, 1 H), 8.83 (s, 1 H); MS m/e 502 (MH⁺).

Example 42



5 ^1H NMR (CDCl_3) δ 2.12-2.15 (m, 2 H), 2.44 (t, $J = 7.0$ Hz, 2 H), 3.02 (s, 3 H), 4.49 (t, $J = 7.4$ Hz, 2 H), 5.23 (s, 2 H), 5.41 (s, 2 H), 7.10-7.14 (m, 1 H), 7.32-7.34 (m, 1 H), 7.43 (dd, $J = 2.4, 9.0$ Hz, 1 H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.92 (d, $J = 8.3$ Hz, 2 H), 8.74 (s, 1 H), 8.80 (s, 1 H);

IR (KBr, cm^{-1}) 3441, 2928, 2244, 1718, 1609, 1492, 1406, 1300, 1150;

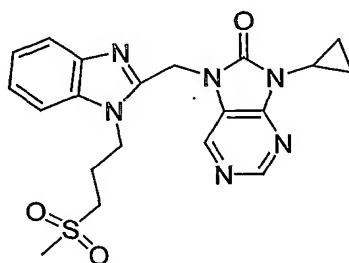
10 MS m/e 520 (MH^+);

Anal. Calcd. for $\text{C}_{25}\text{H}_{22}\text{FN}_3\text{O}_3\text{S}$: C, 57.79; H, 4.26; N, 18.87

Found: C, 57.49; H, 4.11; N, 18.55.

Example 43

15



20 ^1H NMR (CDCl_3) δ 1.17-1.18 (m, 2 H), 2.31-2.37 (m, 2 H), 2.97 (s, 3 H), 3.01-3.06 (m, 1 H), 3.15 (t, $J = 7.2$ Hz, 2 H), 4.58 (t, $J = 7.5$ Hz, 2 H), 5.41 (s, 1 H), 7.30-7.36 (m, 2 H), 7.42 (d, $J = 7.4$ Hz, 1 H), 7.76-7.78 (dd, $J = 1.2, 7.2$ Hz, 1 H), 8.73(s, 1 H), 8.74 (s, 1 H);

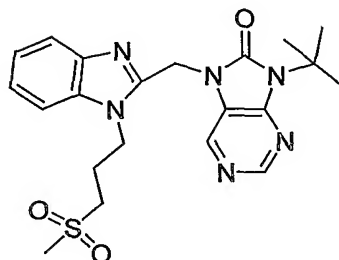
IR (KBr, cm^{-1}) 3424, 1721, 1615, 1493, 1407, 1313, 1126, 750;

MS m/e 427 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{OS} \cdot \text{H}_2\text{O}$: C, 54.04; H, 5.44; N, 18.91

Found: C, 53.95; H, 5.54; N, 18.75.

Example 44



5

^1H NMR (CDCl_3) δ 1.84 (s, 9 H), 2.30-2.35 (m, 2 H), 3.13 (t, $J = 7.2$ Hz, 2H), 4.58 (t, $J = 7.6$ Hz, 2 H), 5.38 (s, 1 H), 7.30-7.35 (m, 2 H), 7.42 (d, $J = 7.4$ Hz, 1 H), 7.76-7.78 (dd, $J = 1.2, 7.2$ Hz, 1 H), 8.66 (s, 1 H), 8.73 (s, 1 H);

10 IR (KBr, cm^{-1}): 3431, 2927, 1718, 1616, 1469, 1444, 1469, 1444, 1296, 1134, 747;

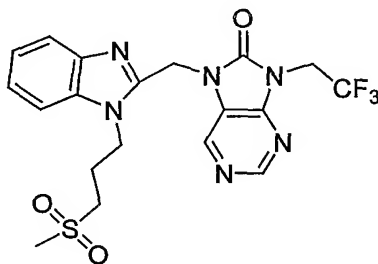
MS m/e 443 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_3\text{S} \cdot \text{H}_2\text{O}$: C, 55.86; H, 6.03; N, 18.61

Found: C, 55.87; H, 5.88; N, 18.44.

15

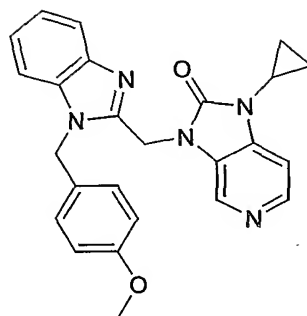
Example 45



^1H NMR (CDCl_3) δ 2.25-2.29 (m, 2 H), 2.97 (s, 3 H), 3.14 (t, $J = 7.0$ Hz, 2 H), 4.56-4.64 (m, 4 H), 5.49 (s, 2 H), 7.32-7.39 (m, 2 H), 7.44 (d, $J = 7.4$ Hz, 1 H), 7.78-7.80 (dd, $J = 1.4, 7.2$ Hz, 1 H), 8.76 (s, 1 H), 8.85 (s, 1 H);

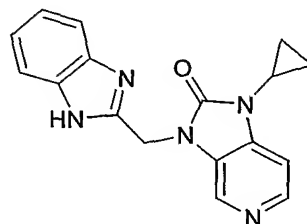
20

MS m/e 469 (MH^+).

Example 46

- 5 ^1H NMR (CDCl_3) δ 0.71-0.74 (m, 2 H), 1.03-1.07 (m, 2 H), 2.63-2.66 (m, 1 H), 3.66 (s, 3 H), 5.39 (s, 2 H), 5.47 (s, 2 H), 6.50 (m, 4 H), 6.99 (d, $J = 5.3$ Hz, 1 H), 7.20 (d, $J = 8.0$ Hz, 1 H), 7.26 (m, 1 H), 7.31 (m, 1 H), 7.85 (d, $J = 8.0$ Hz, 1 H), 8.27 (d, $J = 5.0$ Hz, 1 H), 8.53 (s, 1 H);
MS m/e 426 (MH^+).

10

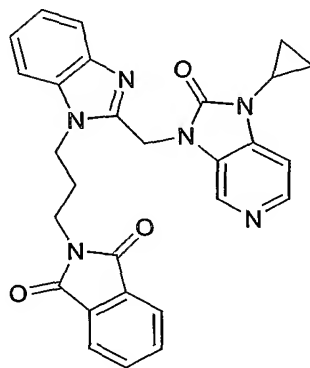
Example 47

- 15 A stirred suspension of Example 46 (11.75 g, 27.6 mmol) in CH_3CN (150 mL) was treated with ceric ammonium nitrate (CAN, 60.60 g, 110 mmol) and diluted with water (25 mL) to give a homogeneous solution which was stirred at room temperature for 24 hours. The mixture was concentrated *in vacuo* to a volume of 50 mL, then diluted with H_2O (100 mL) and again concentrated until
20 100 mL remained and a yellow solid had precipitated from solution. The yellow solid was isolated from the chilled suspension by filtration and was identified as the 4-methoxybenzaldehyde by-product. The filtrate was then diluted with H_2O to 400 mL and MeOH (600 mL) was added. To the resulting solution was added a

saturated aqueous solution of sodium potassium tartrate until the pH of the solution reached 6 and a very finely divided powder precipitated. The reaction mixture was centrifuged and the liquid was decanted away from the solid and concentrated *in vacuo*. The residue was redissolved in water (250 mL) and the
5 resulting solution was extracted with CH₂Cl₂ (8 x 100 mL). The organic extracts were combined and concentrated *in vacuo* to a brown glassy solid which was redissolved in minimum CH₂Cl₂. After a few minutes, a beige powder precipitated from solution. Et₂O was added to the mixture and the solid was isolated by filtration, rinsed with Et₂O, and dried under high vacuum to give 6.62
10 g (79 % yield) of Example 47 as a beige powder.

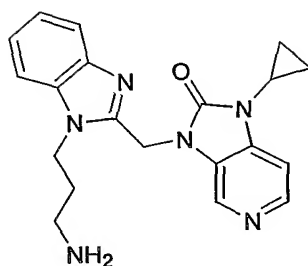
¹H NMR (DMSO-d₆) δ 0.92-0.97 (m, 2 H), 1.06-1.10 (m, 2 H), 2.97-3.01 (m, 1 H), 5.30 (s, 2 H), 7.14-7.17 (m, 2 H), 7.30 (d, J = 5.4 Hz, 1 H), 7.50 (bs, 2 H), 8.25-8.28 (m, 2 H), 12.54 (bs, 1 H);
15 MS m/e 306 (MH⁺).

Example 48



20

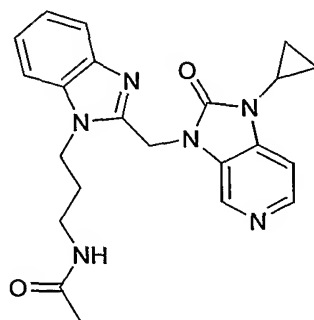
¹H NMR (CDCl₃) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.09-2.15 (m, 2 H), 2.99-3.03 (m, 1 H), 3.82 (t, J = 6.8 Hz, 2 H), 4.42 (t, J = 7.9 Hz, 2 H), 5.36 (s, 2 H), 7.21-7.28 (m, 3 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.69-7.74 (m, 3 H), 7.81-7.85 (m, 2 H), 8.35 (d, J = 5.0 Hz, 1 H), 8.79 (s, 1 H);
25 MS m/e 493 (MH⁺).

Example 49

5 Example **48** (2.58 g, 5.24 mmol) was treated with hydrazine hydrate (2.62 g, 52.4 mmol) in MeOH (100 mL) and the mixture was heated to reflux for 5 hours. The resulting mixture was passed through a 50 mL bed of AG 50W-X2 strong cation exchange resin (Bio-Rad Laboratories), and the bed was rinsed with MeOH (300 mL). The yellow eluent was discarded, and the product was eluted
10 from the resin with 2M ammonia in MeOH (500 mL). The ammonia eluent was concentrated *in vacuo* to give 1.85 g (97 % yield) of Example **49** as an off-white powder.

¹H NMR (DMSO-d₆) δ 0.92 (s, 2 H), 1.07 (d, J = 5.8, 2 H), 1.74 (t, J = 6.8 Hz, 2 H), 2.57 (t, J = 6.2 Hz, 2 H), 2.99-3.01 (m, 1 H), 4.39 (t, J = 7.1 Hz, 2 H), 5.43 (s, 2 H), 7.17 (t, J = 7.4 Hz, 1 H), 7.24 (t, J = 7.5 Hz, 1 H), 7.29 (d, J = 5.1 Hz, 1 H), 7.58 (t, J = 8.6 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.39 (s, 1 H);
15 MS m/e 363 (MH⁺).

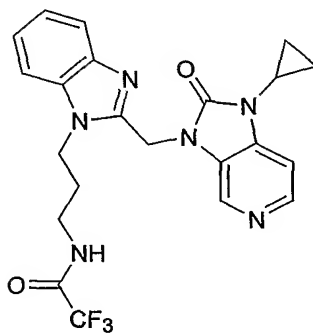
20

Example 50

A mixture of Example 49 (0.050 g, 0.14 mmol) and polystyrene diisopropylethylamine resin (PS-DIEA resin, Argonaut, 0.075 g, 0.28 mmol) in anhydrous CH_2Cl_2 (1 mL) was treated with acetic anhydride (0.141 g, 1.38 mmol) and stirred at room temperature for 18 hours. Solids which precipitated from solution were redissolved by the addition of chloroform (1 mL), and the reaction mixture was filtered to remove the resin. The filtrate was concentrated *in vacuo*, and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.074 g (>100% yield) of the trifluoroacetic acid salt of Example 50 as a glassy, colorless solid.

^1H NMR (DMSO-d_6) δ 0.99-1.02 (m, 2 H), 1.13-1.17 (m, 2 H), 1.84 (s, 3 H), 1.95 (t, $J = 7.3$ Hz, 2 H), 3.14-3.17 (m, 3 H), 4.41 (t, $J = 7.5$ Hz, 2 H), 5.57 (s, 2 H), 7.25 (t, $J = 7.4$ Hz, 1 H), 7.33 (t, $J = 7.4$ Hz, 1 H), 7.58 (d, $J = 8.0$ Hz, 1 H), 7.68 (d, $J = 8.1$ Hz, 1 H), 7.83 (d, $J = 6.4$ Hz, 1 H), 7.99 (t, $J = 5.2$ Hz, 1 H), 8.62 (d, $J = 6.2$ Hz, 1 H), 8.83 (s, 1 H);
MS m/e 405 (MH^+).

Example 51

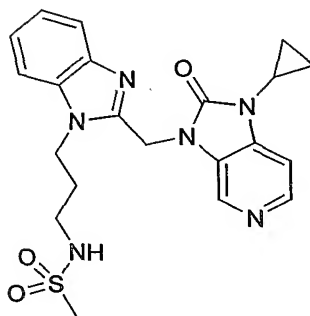


Example 51 was prepared according to the same procedure described for Example 50 using trifluoroacetic anhydride.

^1H NMR (DMSO-d_6) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.03-2.08 (m, 2 H), 3.14-3.18 (m, 1 H), 3.33-3.37 (m, 2 H), 4.42 (t, $J = 7.5$ Hz, 2 H), 5.54 (s, 2 H), 7.20-7.23 (m, 1 H), 7.29-7.23 (m, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 7.65 (d, $J = 8.1$

Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.81 (s, 1 H), 9.54-9.56 (m, 1 H);
MS m/e 459 (MH⁺).

5

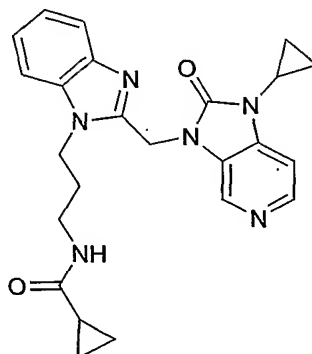
Example 52

Example 52 was prepared according to the same procedure described for
10 Example 50 using methanesulfonyl chloride.

¹H NMR (DMSO-d₆) δ 1.04-1.07 (m, 2 H), 1.14-1.17 (m, 2 H), 2.12 (t, J = 7.4 Hz, 2 H), 2.96 (s, 3 H), 3.16-3.18 (m, 3 H), 4.58 (t, J = 7.6 Hz, 2 H), 5.82 (s, 2 H), 7.23-7.25 (m, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.54 (t, J = 7.7 Hz, 1 H), 7.75 (d, J =
15 8.1 Hz, 1 H), 7.88 (d, J = 6.5 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1 H), 8.66 (d, J = 6.5 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 441 (MH⁺).

Example 53

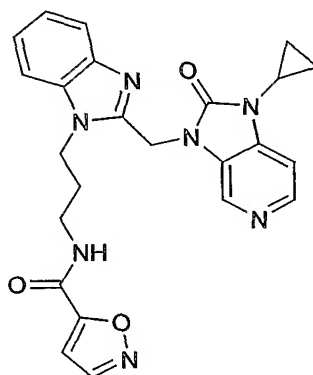
20



Example 53 was prepared according to the same procedure described for Example 50 using cyclopropanecarbonyl chloride.

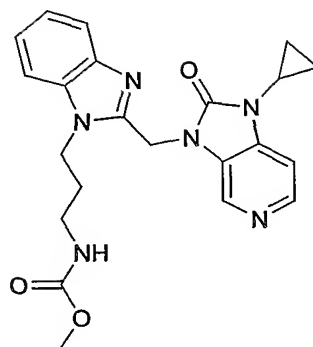
¹H NMR (DMSO-d₆) δ 0.63-0.69 (m, 4 H), 0.98-1.02 (m, 2 H), 1.13-1.17 (m, 2 H), 1.53-1.58 (m, 1 H), 1.94-2.00 (m, 2 H), 3.14-3.20 (m, 3 H), 4.40 (t, J = 7.4 Hz, 2 H), 5.55 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 6.3 Hz, 1 H), 8.21 (t, J = 5.1 Hz, 1 H), 8.61 (d, J = 6.2 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 431 (MH⁺).

Example 54



Example 54 was prepared according to the same procedure described for Example 50 using isoxazole-5-carbonyl chloride.

¹H NMR (DMSO-d₆) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.06-2.12 (m, 2 H), 3.13-3.17 (m, 1 H), 3.39-3.43 (m, 2 H), 4.46 (t, J = 7.5 Hz, 2 H), 5.56 (s, 2 H), 7.06 (s, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 6.2 Hz, 1 H), 8.75 (s, 1 H), 8.81 (s, 1 H), 9.08 (t, J = 5.5 Hz, 1 H);
MS m/e 458 (MH⁺).

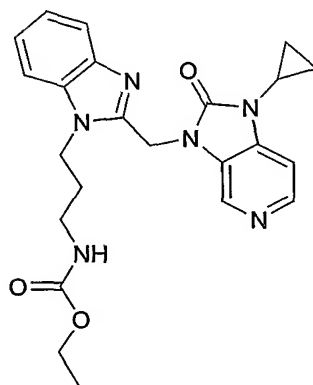
Example 55

5 Example **55** was prepared according to the same procedure described for Example **50** using methyl chloroformate.

^1H NMR (DMSO- d_6) δ 0.90-0.93 (m, 2 H), 1.03-1.09 (m, 2 H), 1.80-1.86 (m, 2 H), 2.98-3.02 (m, 1 H), 3.05-3.08 (m, 2 H), 3.53 (s, 3 H), 4.35 (t, $J = 7.5$ Hz, 2 H),
10 5.38 (s, 2 H), 7.17 (t, $J = 7.7$ Hz, 1 H), 7.23-7.29 (m, 3 H), 7.57 (d, $J = 8.2$ Hz, 2 H), 8.25 (d, $J = 5.0$ Hz, 1 H), 8.40 (s, 1 H);
MS m/e 421 (MH^+).

Example 56

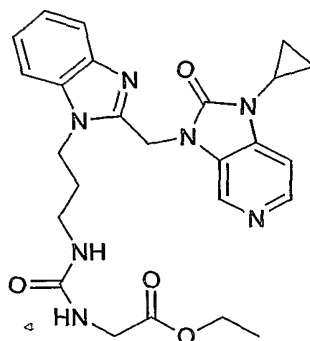
15



Example **56** was prepared according to the same procedure described for Example **50** using ethyl chloroformate.

^1H NMR ($\text{DMSO}-d_6$) δ 0.89-0.94 (m, 2 H), 1.03-1.09 (m, 2 H), 1.16 (t, $J = 7.1$ Hz, 3 H), 1.80-1.86 (m, 2 H), 2.98-3.03 (m, 1 H), 3.04-3.08 (m, 2 H), 4.00 (q, $J = 7.1$ Hz, 2 H), 4.35 (t, $J = 7.5$ Hz, 2 H), 5.39 (s, 2 H), 7.23-7.29 (m, 3 H), 7.29 (d, $J = 5.2$ Hz, 1 H), 7.57 (d, $J = 8.8$ Hz, 2 H), 8.25 (d, $J = 5.1$ Hz, 1 H), 8.40 (s, 1 H);
5 MS m/e 435 (MH^+).

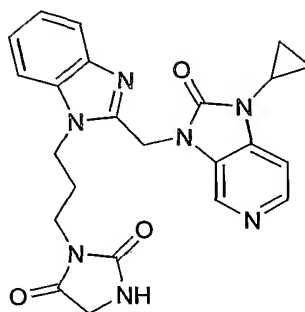
Example 57



10

A solution of Example 49 (0.050 g, 0.14 mmol) in chloroform (2 mL) was treated with ethyl isocyanatoacetate (0.018 g, 0.14 mmol) and stirred for 15 minutes at room temperature. The mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.080 g (96 % yield) of the trifluoroacetic acid salt of Example 57 as a glassy, colorless solid.
15

^1H NMR ($\text{DMSO}-d_6$) δ 0.98-1.02 (m, 2 H), 1.13-1.17 (m, 5 H), 1.91-1.97 (m, 2 H), 3.10-3.12 (m, 2 H), 3.15-3.18 (m, 1 H), 3.76 (s, 2 H), 4.04 (q, $J = 7.1$ Hz, 2 H),
20 4.39 (t, $J = 7.5$ Hz, 2 H), 5.55 (s, 2 H), 6.31 (bs, 1 H), 6.43 (bs, 1 H), 7.23 (t, $J = 7.6$ Hz, 1 H), 7.29-7.33 (m, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 7.66 (d, $J = 8.1$ Hz, 1 H), 7.83 (d, $J = 6.3$ Hz, 1 H), 8.62 (d, $J = 5.8$ Hz, 1 H), 8.83 (s, 1 H);
MS m/e 492 (MH^+).

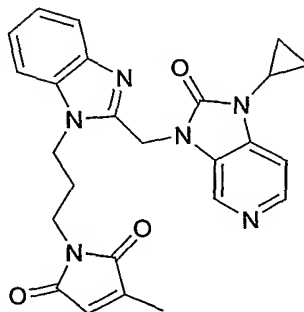
Example 58

5 Example 57 (0.061 g, 0.14 mmol) was dissolved in glacial acetic acid (2 mL) and the resulting solution was heated to 120 °C in a sealed tube for several hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 0.036 g (47 % yield) of the trifluoroacetic acid
10 salt of Example 58 as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.01-2.07 (m, 1 H), 3.13-3.18 (m, 2 H), 3.52 (t, J = 6.8 Hz, 2 H), 3.92 (s, 2 H), 4.38-4.43 (m, 2 H), 5.55 (s, 2 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.29-7.33 (m, 1 H), 7.56-7.59 (m, 1 H),
15 7.67 (d, J = 8.0 Hz, 1 H), 7.81-7.83 (m, 1 H), 8.09 (s, 1 H), 8.60-8.62 (m, 1 H), 8.80-8.82 (m, 1 H);
MS m/e 446 (MH⁺).

Example 59

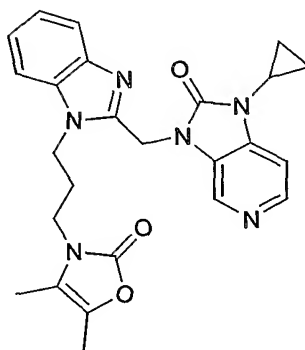
20



Example 49 (0.050 g, 0.14 mmol) was combined with citraconic anhydride (0.017 g, 0.15 mmol) and glacial acetic acid (2 mL). The resulting mixture was heated to 80 °C for 18 hours and then concentrated *in vacuo*. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) gave 0.052g (66 % yield) of the trifluoroacetic acid salt of Example 59 as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.00 (s, 3 H), 2.00-2.06 (m, 2 H), 3.12-3.17 (m, 1 H), 3.56 (t, J = 6.8 Hz, 2 H), 4.40 (t, J = 7.7 Hz, 2 H), 5.51 (s, 2 H), 6.62-6.63 (m, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.3 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 6.2 Hz, 1 H), 8.59 (d, J = 4.7 Hz, 1 H), 8.80 (s, 1 H); MS m/e 457 (MH⁺).

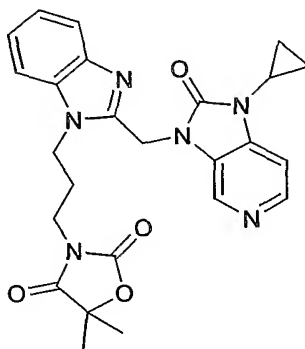
15

Example 60

Example 49 (0.050g, 0.14 mmol) was combined with 4,5-dimethyl-1,3-dioxo-2-one (0.016 g, 0.14 mmol), sodium bicarbonate (0.024 g, 0.14 mmol) and anhydrous DMF (2 mL), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 0.029 g (37 % yield) of the trifluoroacetic acid salt of Example 60 as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.98-1.00 (m, 2 H), 1.13-1.17 (m, 2 H), 1.96 (s, 3 H), 2.00 (s, 3 H), 2.06-2.12 (m, 2 H), 3.13-3.18 (m, 1 H), 3.61 (t, J = 7.3 Hz, 2 H), 4.44 (t, J = 7.7 Hz, 2 H), 5.54 (s, 2 H), 7.22 (t, J = 7.3 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.0 Hz, 1 H), 8.61 (d, J = 5.3 Hz, 1 H), 8.81 (s, 1 H);
MS m/e 459 (MH⁺).

Example 61



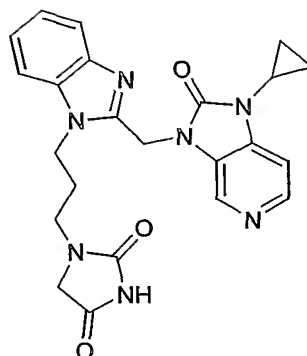
10

Example 49 (0.050 g, 0.14 mmol) was combined with methyl-2-hydroxyisobutyrate (0.018 g, 0.14 mmol), a catalytic amount of 50 % sodium methoxide in MeOH and diethyl carbonate (1 mL) in a sealed tube and the mixture was heated to 175 °C for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 0.018 g (21 % yield) of the trifluoroacetic acid salt of Example 61 as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.99-1.01 (m, 2 H), 1.13-1.15 (m, 2 H), 1.52 (s, 6 H), 2.11 (t, J = 7.5 Hz, 2 H), 3.14-3.16 (m, 1 H), 3.60 (t, J = 6.9 Hz, 2 H), 4.46 (t, J = 7.7 Hz, 2 H), 5.54 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.1 Hz, 1 H), 8.61 (s, 1 H), 8.81 (s, 1 H);
MS m/e 475 (MH⁺).

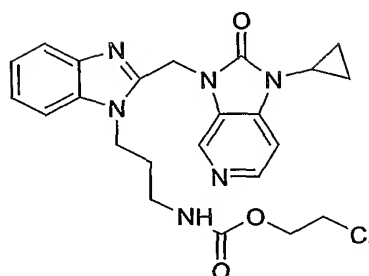
25

Example 62



- 5 Example 49 (0.050 g, 0.14 mmol) was combined with N-chloroacetyl urethane (0.024 g, 0.14 mmol), sodium bicarbonate (0.023g, 0.28 mmol) and anhydrous acetonitrile (2 mL) in a sealed tube. The mixture was heated to 140 °C for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90%
10 MeOH in H₂O with 0.1% TFA) to give 0.030 g (39 % yield) of the trifluoroacetic acid salt of Example 62 as a glassy, colorless solid.

- ¹H NMR (DMSO-d₆) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.00-2.06 (m, 2 H), 3.13-3.18 (m, 1 H), 3.41 (t, J = 6.8 Hz, 2 H), 4.00 (s, 2 H), 4.41 (t, J = 7.7 Hz, 2 H), 5.56 (s, 2 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 6.0 Hz, 1 H), 8.80 (s, 1 H), 10.77 (s, 1 H);
15 MS m/e 446 (MH⁺).

Example 63

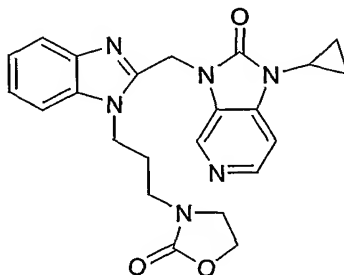
5 A mixture of Example 49 (100 mg, 0.27 mmol) and 2-bromoethylchloroformate (51.7 mg, 0.27 mmol) was stirred at room temperature for 18 hours. The reaction mixture was filtered to remove inorganic impurities and the solid was washed with MeOH. The MeOH solution was concentrated to give 126 mg (99% yield) of Example 63 as a hygroscopic solid.

10

^1H NMR (DMSO- d_6) δ 0.94 (bs, 2 H), 1.10 (d, $J = 5.4$ Hz, 2 H), 1.21 (d, $J = 6.4$ Hz, 2 H), 1.86-1.89 (m, 2 H), 3.09-3.11 (m, 1 H), 3.78-3.80 (m, 1 H), 3.85-3.87 (m, 1 H), 4.21-4.23 (m, 2 H), 4.35-4.37 (m, 2 H), 5.43 (s, 2 H), 7.18 (t, $J = 7.7$ Hz, 1 H), 7.25 (t, $J = 7.5$ Hz, 1 H), 7.46-7.50 (m, 2 H), 7.55-7.60 (m, 1 H), 8.37 (d, $J =$

15

5.0 Hz, 1 H), 8.54 (s, 1 H);
MS m/e 469 (MH^+).

Example 64

20

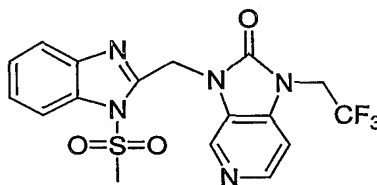
A mixture of Example 63 (70 mg, 0.149 mmol) and lithium bis(trimethylsilyl)amide (0.15 mL, 0.149 mmol) was stirred at reflux in dioxane

(15 mL) for 16 hours. The solvent was evaporated and the residue was diluted with EtOAc, washed with H₂O, dried over Na₂SO₄, and evaporated to give 41 mg (63% yield) of Example 64.

- 5 ¹H NMR (DMSO-d₆) δ 0.90-0.93 (m, 2 H), 1.01-1.09 (m, 2 H), 1.92-1.98 (m, 2 H), 2.98-3.03 (m, 1 H), 3.27 (t, J = 6.9 Hz, 2 H), 3.55 (t, J = 8.1 Hz, 2 H), 4.27 (t, J = 7.7 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 5.40 (s, 2 H), 7.17-7.20 (t, J = 7.4 Hz, 1 H), 7.22-7.29 (m, 2 H), 7.56-7.62 (m, 2 H), 8.25 (d, J = 5.3 Hz, 1 H), 8.42 (s, 1 H); MS m/e 416 (MH⁺).

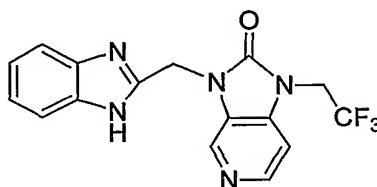
10

Example 65



- 15 MS m/e 426 (MH⁺).

Example 66



20

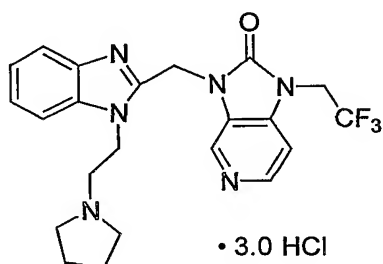
Example 65 was refluxed with hydrazine hydrate (5 mL) in MeOH (10 mL) for 1 hour. The solvent was evaporated and the oily residue was diluted with water and extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and evaporated to give 467 mg (29% yield) of Example 66.

25

^1H NMR (DMSO- d_6) δ 4.91 (q, J = 9.3 Hz, 2 H), 5.38 (s, 2 H), 7.12-7.21 (m, 2 H), 7.44 (d, J = 5.3 Hz, 1 H), 7.45-7.50 (m, 1 H), 7.51-7.58 (m, 1 H), 8.32 (d, J = 5.3 Hz, 1 H), 8.38 (s, 1 H), 12.60 (s, 1 H);

MS m/e 348 (MH^+).

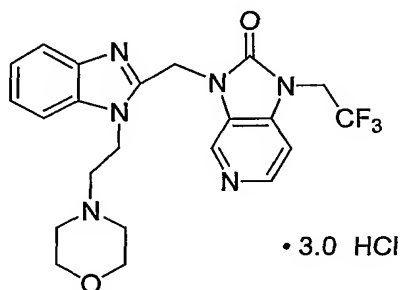
5

Example 67

10 ^1H NMR (DMSO- d_6) δ 1.88-2.01 (m, 2 H), 2.01-2.13 (m, 2 H), 3.10-3.22 (m, 2 H), 3.58-3.65 (m, 2 H), 3.70-3.79 (m, 2 H), 4.90-4.99 (m, 2 H), 5.10-5.23 (m, 2 H), 5.95 (s, 2 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 6.1 Hz, 1 H), 8.76 (d, J = 6.4 Hz, 1 H), 9.18 (s, 1 H);

15 IR (KBr, cm^{-1}) 3416, 2927, 1754, 1653, 1627, 1518, 1462, 1264, 1168, 1121, 831, 755.

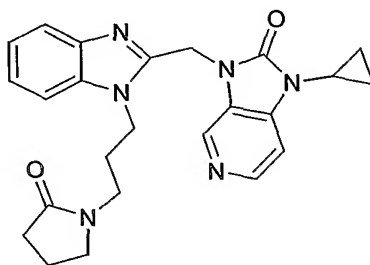
MS m/e 445 (MH^+).

Example 68

20

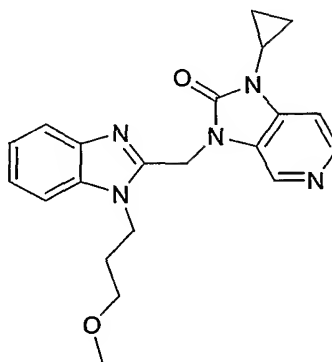
¹H NMR (DMSO-d₆) δ 3.19-3.31 (m, 2 H), 3.56-3.63 (m, 2 H), 3.65-3.74 (m, 2 H), 3.86-3.95 (m, 2 H), 4.00-4.09 (m, 2 H), 5.01 (t, J = 7.5 Hz, 2 H), 5.16 (q, J = 9.0 Hz, 2 H), 5.93 (s, 2 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 1 H), 7.99 (d, J = 7.9 Hz, 1 H), 8.08 (d, J = 6.1 Hz, 1 H), 8.75 (d, J = 6.4 Hz, 1 H), 9.18 (s, 1 H);
IR (KBr, cm⁻¹) 3430, 1761, 1618, 1517, 1268, 1172, 823, 770;
MS m/e 461 (MH⁺).

Example 69



¹H NMR (DMSO-d₆) δ 1.03-1.08 (m, 2 H), 1.12-1.16 (m, 2 H), 2.01-2.17 (m, 2 H), 2.21-2.31 (m, 2 H), 2.31-2.41 (m, 2 H), 3.21-3.35 (m, 3 H), 3.40-50 (m, 1 H), 3.61-3.72 (m, 1 H), 4.45-4.51 (m, 2 H), 5.77(s, 2 H), 7.41-7.48 (m, 2 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.85-7.88 (m, 2 H), 8.64 (d, J = 6.7 Hz, 1 H), 8.95 (s, 1 H); MS m/e 430 (MH⁺).

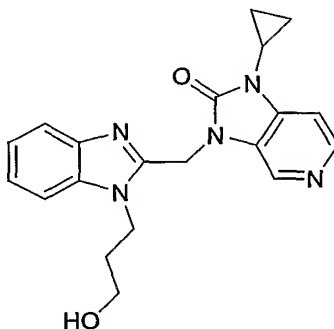
Example 70



^1H NMR (CDCl_3) δ 1.14 (q, $J = 7.5$ Hz, 2 H), 1.21 (q, $J = 6.4$ Hz, 2 H), 2.20-2.23 (m, 2 H), 3.07 (m, 1 H), 3.38 (s, 3 H), 3.38 (t, $J = 5.4$ Hz, 2 H), 4.56 (t, $J = 6.5$ Hz, 2 H), 5.85 (s, 2 H), 7.40 (t, $J = 7.6$ Hz, 1 H), 7.45 (t, $J = 7.7$ Hz, 1 H), 7.53-7.55 (m, 2 H), 7.88 (d, $J = 8.2$ Hz, 1 H), 8.38 (d, $J = 6.3$ Hz, 1 H), 8.92 (s, 1 H);

5 MS m/e 378 (MH^+).

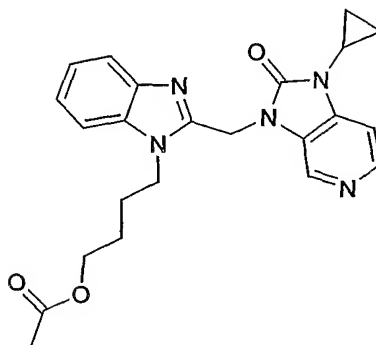
Example 71



10

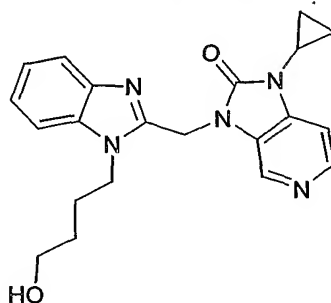
A solution of Example 70 (434 mg, 0.72 mmol) in CH_2Cl_2 (25 mL) was treated with boron tribromide (1M in CH_2Cl_2 , 7.2 mL, 7.2 mmol). The reaction mixture was stirred at room temperature for 40 minutes and then was quenched slowly with anhydrous MeOH. The solvent was evaporated and the residue was diluted with MeOH and evaporated two more times. Purification by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) gave Example 71.

15 ^1H NMR ($\text{DMSO}-d_6$) δ 1.07 (d, $J = 5.6$ Hz, 2 H), 1.83 (t, $J = 6.2$ Hz, 2 H), 2.99 (t, $J = 3.2$ Hz, 1 H), 3.17 (d, $J = 5.0$ Hz, 1 H), 3.40 (t, $J = 5.4$ Hz, 2 H), 4.40 (t, $J = 6.8$ Hz, 2 H), 4.75 (t, $J = 4.6$, 1 H), 5.42 (s, 2 H), 7.16 (t, $J = 7.5$ Hz, 1 H), 7.24 (t, $J = 7.6$ Hz, 1 H), 7.29 (d, $J = 4.8$ Hz, 1 H), 7.56 (d, $J = 8.1$ Hz, 2 H), 8.25 (s, 1 H), 8.38 (s, 1 H);
20 MS m/e 364 (MH^+).

Example 72

- 5 ^1H NMR (CDCl_3) δ 0.99-1.03 (m, 2 H), 1.16-1.20 (m, 2 H), 1.65-1.69 (m, 2 H), 1.71-1.75 (m, 2 H), 2.00 (s, 3 H), 2.92-2.95 (m, 1 H), 4.03 (t, $J = 6.2$ Hz, 2 H), 4.35 (t, $J = 7.3$ Hz, 2 H), 5.37 (s, 2 H), 7.14 (d, $J = 5.0$ Hz, 1 H), 7.26-7.32 (m, 3 H), 7.56-7.77 (m, 1 H), 8.32 (d, $J = 5.4$ Hz, 1 H), 8.72 (s, 1 H);
MS m/e 420 (MH^+).

10

Example 73

- Example 72 (1.0 g, 2.48 mmol) and K_2CO_3 (1.03 g, 7.44 mmol) were
15 stirred together in MeOH (5 mL) at room temperature for 1.5 hours. The mixture
was diluted with H_2O and extracted with CH_2Cl_2 (3 x 25 mL). The combined
extracts were washed with brine, dried over MgSO_4 , and evaporated. The product
was then recrystallized from MeOH to give 650 mg (70% yield) of Example 73.
Example 73 was converted to the HCl salt by treating a solution of 73 in MeOH
20 with 4 N HCl in dioxane and then by evaporating the solvent.

¹H NMR (DMSO-d₆) δ 1.03-1.06 (m, 2 H), 1.12-1.16 (m, 2 H), 1.50-1.56 (m, 2 H), 1.89-1.83 (m, 2 H), 3.13-3.17 (m, 1 H), 3.46 (t, J = 6.3 Hz, 2 H), 4.46 (t, J = 7.5 Hz, 2 H), 5.70 (s, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.81 (d, J = 6.4 Hz, 1 H), 8.61 (d, J = 6.4 Hz, 1 H), 8.93 (s, 1 H);

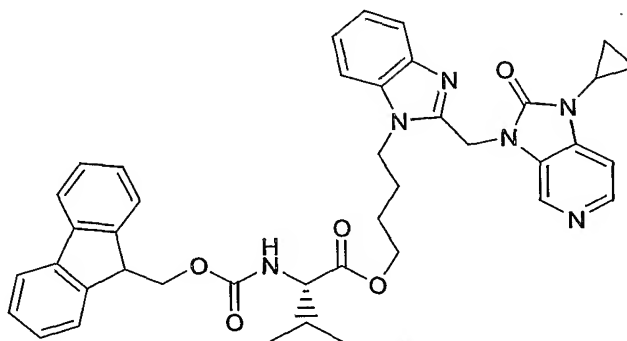
IR (KBr, cm⁻¹) 3350, 2907, 2443, 1736, 1516, 1421, 1172, 825;

MS m/e 378 (MH⁺).

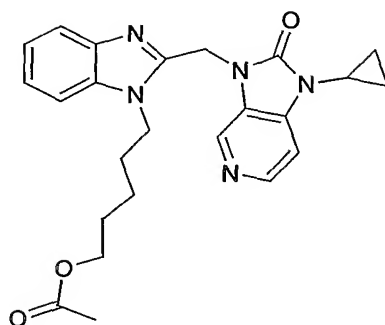
Anal. Calcd for C₂₉H₃₀N₄O₃•1.25 HCl: C, 59.63; H, 5.78; N, 16.56

Found: C, 59.52; H, 5.88; N, 16.57.

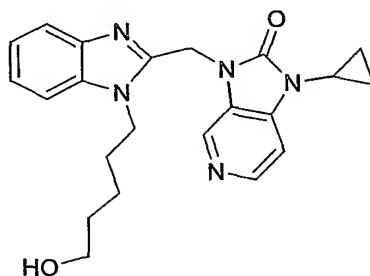
Example 74



Fmoc-L-valine (0.690 g, 2.00 mmol) was combined with oxalyl chloride (0.508 g, 4.00 mmol) and dichloromethane (10 mL), and the resulting solution was stirred for 2 hours. The mixture was concentrated *in vacuo* to a yellow oil, which was then combined with Example 73 (0.252 g, 0.667 mmol) in dry CH₃CN (15 mL). The resulting mixture was stirred for 72 hours, then was diluted with H₂O (5 mL) and was concentrated *in vacuo*. The mixture was redissolved in EtOAc (50 mL) and the solution was washed successively with saturated aqueous NaHCO₃ (3 x 10 mL) and brine (10 mL). The aqueous extracts were combined and back-extracted with EtOAc. The combined organic extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. Purification of the crude material by flash chromatography (CH₂Cl₂:MeOH, 25:1) gave 410 mg of Example 74 as an off-white solid which was used immediately upon isolation.

Example 76

- 5 ^1H NMR (DMSO- d_6) δ 0.89-0.93 (m, 2 H), 1.06-1.08 (m, 2 H), 1.31-1.34 (m, 2 H), 1.54-1.58 (m, 2 H), 1.58-1.66 (m, 2 H), 1.98 (s, 3 H), 2.97-3.00 (m, 1 H), 3.96 (t, $J = 6.6$ Hz, 2 H), 4.32 (t, $J = 7.5$ Hz, 1 H), 5.39 (s, 2 H), 7.16 (t, $J = 7.2$ Hz, 1 H), 7.24 (t, $J = 7.0$ Hz, 1 H), 7.29 (d, $J = 5.0$ Hz, 1 H), 7.58 (t, $J = 7.8$ Hz, 2 H), 8.22 (bs, 1 H), 8.42 (bs, 1 H);
- 10 MS m/e 433 (MH^+).

Example 77

15

Example 76 (115 mg, 0.27 mmol) in 1 N HCl (20 mL) was heated to reflux for 1 hour then concentrated. The oily residue was triturated with EtOAc/MeOH to give 106 mg (94% yield) of Example 77 106 mg (94% yield) as the HCl salt.

20

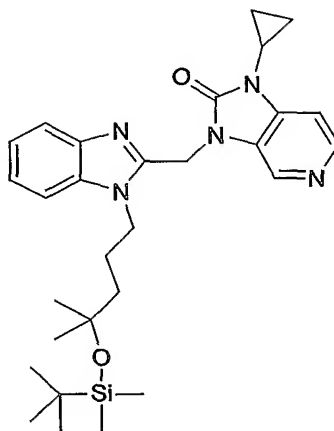
^1H NMR (DMSO- d_6) δ 1.04-1.10 (m, 2 H), 1.10-1.17 (m, 2 H), 1.42-1.53 (m, 4 H), 1.85-1.91 (m, 2 H), 3.13-3.17 (m, 1 H), 3.40-3.50 (m, 2 H), 4.51 (t, $J = 7.5$ Hz,

2 H), 5.82 (s, 2 H), 7.43-7.46 (m, 1 H), 7.46-7.52 (m, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 6.4 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.64 (d, J = 6.4 Hz, 1 H), 8.97 (s, 1 H);

MS m/e 391 (MH⁺).

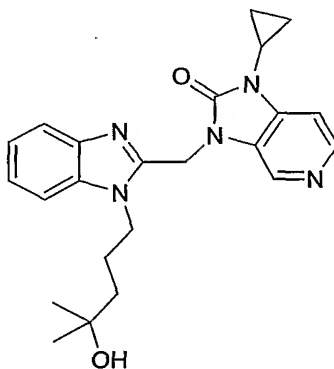
5

Example 78



10 Example 78 was prepared according to the general coupling procedure shown in Scheme I-C and was used immediately upon isolation.

Example 79



15

To a solution of Example 79 (86 mg, 0.17 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.25 mL, 0.25 mmol).

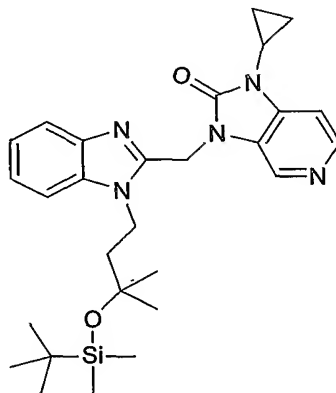
The reaction mixture was stirred at room temperature for 18 hours at which time more tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.50 mL, 0.50 mmol) was added and stirring was continued at room temperature for an additional 18 hours. Purification by flash column chromatography (CH₂Cl₂/MeOH, 9:1) gave

5 Example 79.

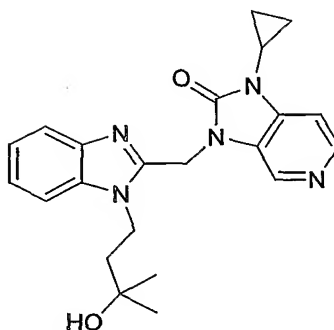
¹H NMR (CDCl₃) δ 0.94-0.97 (m, 2 H), 1.07 (s, 6 H), 1.09-1.11 (m, 2 H), 1.40 (t, J = 3.6 Hz, 2 H), 1.67-1.70 (m, 1 H), 2.86-2.87 (m, 1 H), 4.25 (t, J = 7.7 Hz, 2 H), 5.31 (s, 2 H), 7.05 (d, J = 5.3 Hz, 1 H), 7.18-7.21 (m, 2 H), 7.27 (t, J = 4.6 Hz, 1 H), 7.71 (t, J = 4.6 Hz, 1 H), 8.24 (d, J = 5.3 Hz, 1 H), 8.65 (s, 1 H);
10 IR (KBr, cm⁻¹) 3373, 2966, 1720, 1609, 1499, 1410, 913, 742;
MS m/e 406 (MH⁺).

Example 80

15



Example 80 was prepared according to the general coupling procedure shown in Scheme I-C and was used immediately upon isolation.

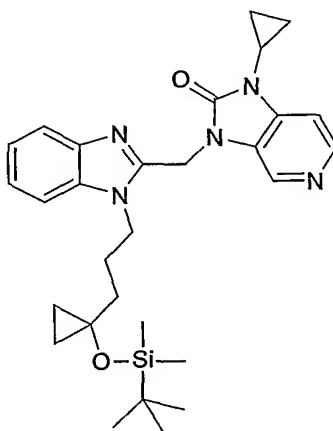
Example 81

5 Example 81 was prepared according to the same deprotection procedure as Example 79 from Example 80.

¹H NMR (CDCl₃) δ 1.02-1.04 (m, 2 H), 1.16 (q, J = 6.9 Hz, 2 H), 1.32 (s, 6 H),
1.81 (t, J = 3.2 Hz, H), 2.49 (s, 1 H), 2.93 (m, 1 H), 4.45 (t, J = 3.4 Hz, 2 H), 5.41
10 (s, 2 H), 7.14 (d, J = 5.25 Hz, 1 H), 7.27-7.30 (m, 2 H), 7.33 (dd, J = 2.5, 3.5 Hz, 1
H), 7.77 (dd, J = 2.9, 3.1 Hz, 1 H), 8.34 (d, J = 5.3, 1 H), 8.77 (s, 1 H);
MS m/e 392 (MH⁺).

Example 82

15



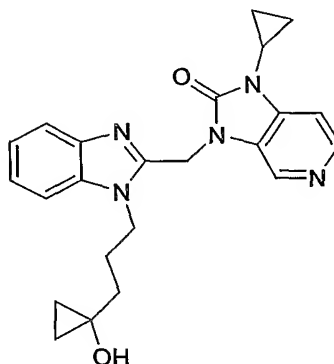
¹H NMR (CDCl₃) δ 0.03 (s, 6 H), 0.80-0.86 (m, 2 H), 0.89 (s, 9 H), 1.00-1.02 (m,
2 H), 1.15-1.17 (m, 2 H), 1.48-1.51 (m, 2 H), 1.77-1.86 (m, 2 H), 2.05 (t, J = 7.4

Hz, 2 H), 2.89-2.97 (m, 1 H), 4.29 (t, $J = 7.4$ Hz, 2 H), 5.35 (s, 2 H), 7.10 (d, $J = 5.2$ Hz, 1 H), 7.24-7.26 (m, 2 H), 7.31-7.33 (m, 1 H), 7.74-7.77 (m, 1 H), 8.31 (d, $J = 5.2$ Hz, 1 H), 8.69 (s, 1 H);

MS m/e 518 (MH^+).

5

Example 83



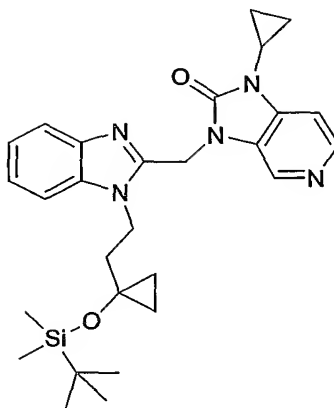
10 Example 83 was prepared from Example 82 according to the same deprotection procedure described for Example 79.

1H NMR ($DMSO-d_6$) δ 0.91-1.05 (m, 4 H), 1.13-1.22 (m, 2 H), 1.77-1.84 (m, 2 H), 2.27 (q, $J = 7.4$ Hz, 2 H), 2.39 (t, $J = 6.8$ Hz, 2 H), 2.89-2.95 (m, 1 H), 4.23 (t, $J = 7.7$ Hz, 2 H), 5.27 (s, 2 H), 7.03 (d, $J = 5.1$ Hz, 1 H), 7.24-7.31 (m, 2 H), 7.34 (dd, $J = 1.9, 6.4$ Hz, 1 H), 7.66 (dd, $J = 1.4, 7.1$ Hz, 1 H), 8.23 (d, $J = 5.2$ Hz, 1 H), 8.60 (s, 1 H);

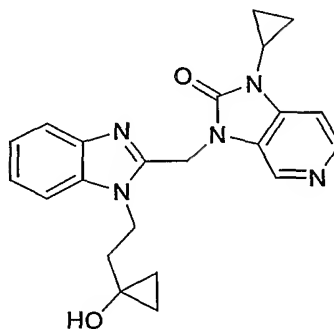
IR (KBr, cm^{-1}) 3392, 2938, 1721, 1609, 1499, 1410, 913, 743;

MS m/e 404 (MH^+).

15

Example 84

- 5 ^1H NMR (CDCl_3) δ 0.05 (t, $J = 5.8$ Hz, 2 H), 0.14 (s, 6 H), 0.63 (t, $J = 6.1$ Hz, 2 H), 0.90 (s, 9 H), 1.00-1.03 (m, 2 H), 1.13-1.17 (m, 2 H), 1.86 (t, $J = 6.6$ Hz, 2 H), 2.89-2.92 (m, 1 H), 4.61 (t, $J = 6.6$ Hz, 2 H), 5.42 (s, 2 H), 7.12 (d, $J = 4.9$ Hz, 1 H), 7.22-7.24 (m, 2 H), 7.38-7.40 (m, 1 H), 7.72-7.74 (m, 1 H), 8.32 (d, $J = 5.5$ Hz, 1 H), 8.66 (s, 1 H);
- 10 MS m/e 504 (MH^+).

Example 85

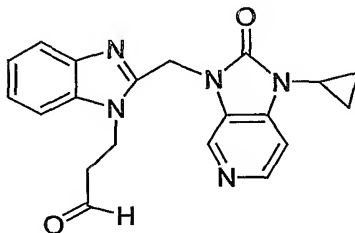
15

Example 85 was prepared from Example 84 according to the same deprotection procedure described for Example 79.

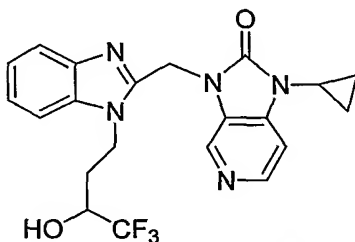
- ^1H NMR ($\text{DMSO}-d_6$) δ 0.10 (q, $J = 4.8$ Hz, 2 H), 0.49 (q, $J = 4.9$ Hz, 2 H), 0.90-0.94 (m, 2 H), 1.04-1.07 (m, 2 H), 1.85 (t, $J = 7.0$ Hz, 2 H), 2.99 (m, 1 H), 4.54 (t,
- 20

$J = 7.0$ Hz, 2 H), 5.42 (s, 1 H), 5.46 (s, 2 H), 7.16 (dt, $J = 1.0, 7.6$ Hz, 1 H), 7.23 (dt, $J = 1.0, 7.6$ Hz, 1 H), 7.28 (d, $J = 5.2$ Hz, 1 H), 7.54 (dd, $J = 8.0, 23.0$ Hz, 2 H), 8.25 (d, $J = 5.25$ Hz, 1 H), 8.39 (s, 1 H);
MS m/e 390 (MH^+).

5

Example 86

10 To a solution of oxalyl chloride (326 mg, 2.57 mmol) in CH_2Cl_2 (5 mL) cooled to -78 °C with a dry ice/acetone bath was added a solution of DMSO (268 mg, 3.42 mmol) in CH_2Cl_2 (10 mL) slowly over 15 minutes. After stirring for 10 minutes, a solution of Example 71 (622 mg, 1.71 mmol) in CH_2Cl_2 (5 mL) was slowly added to the reaction mixture. The reaction was monitored for completion
15 by thin layer chromatography and LC/MS. The solution became cloudy upon completion and the reaction was quenched at -78 °C by adding triethylamine (693 mg, 6.85 mmol). The solution became clear and was then warmed to room temperature. The reaction mixture was diluted with more CH_2Cl_2 , washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by flash column
20 chromatography (gradient, EtOAc/MeOH, 10:1 to 3:1) gave 185 mg (19% yield) of Example 86 which was used immediately upon isolation.

Example 87

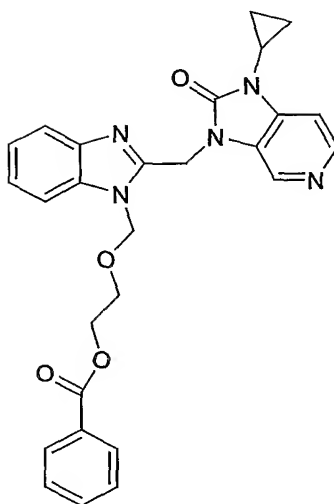
25

Example **87** was prepared according to the procedure described in *J. Med. Chem.*, **1996**, 39, 2411-2421 by Yu, K.-L. et al. using aldehyde **86**:

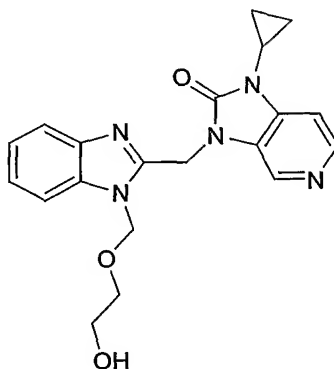
5 A fresh solution of anhydrous 1M tetrabutylammonium fluoride in THF was prepared according to the procedure described by Cox et al in *J. Organic Chemistry*, **1984**, 49, 3219-3220.

To a solution of Example **86** (150 mg, 0.42 mmol) in THF (10 mL) was added trimethyl(trifluoromethyl) silane (0.5M in THF, 1.25 mL, 0.62 mmol) followed by a catalytic amount of tetrabutylammonium fluoride (TBAF, 1M in THF, 8 μ L) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 hours and then warmed to room temperature. Additional trimethyl(trifluoromethyl) silane (0.5M in THF, 1.05 mL, 0.53 mmol) and TBAF (1M in THF, 8 μ L) were added to push the reaction toward completion. The reaction was quenched with excess TBAF (1M in THF, 2.88 mL, 2.88 mmol) and the reaction mixture was allowed to stir for 18 hours. The solvent was evaporated and the residue was purified by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) to give 106 mg (59% yield) of Example **87**.

20 ^1H NMR (CD_3OD) δ 0.98-1.07 (m, 2 H), 1.08-1.16 (m, 1 H), 1.89-1.97 (m, 1 H), 2.08-2.14 (m, 1 H), 2.99-3.04 (m, 2 H), 3.91-3.95 (m, 1 H), 4.53-4.63 (m, 2 H), 5.46-5.55 (m, 2 H), 7.25-7.28 (m, 1 H), 7.33 (dt, $J = 0.9, 7.8$ Hz, 1 H), 7.40 (d, $J = 5.5$ Hz, 1 H), 7.58 (d, $J = 8.1$ Hz, 2 H), 8.26 (d, $J = 5.4$ Hz, 1 H), 8.30 (s, 1 H); IR (KBr, cm^{-1}) 3422, 1723, 1613, 1504, 1412, 1173, 1131, 745;
25 MS m/e 432 (MH^+).

Example 88

- 5 ^1H NMR (CDCl_3) δ 0.92-0.95 (m, 2 H), 1.03-1.07 (m, 2 H), 2.81-2.85 (m, 1 H), 3.53 (t, $J = 4.8$ Hz, 2 H), 4.07 (t, $J = 4.8$ Hz, 2 H), 5.36 (s, 2 H), 5.69 (s, 2 H), 7.04 (d, $J = 5.5$ Hz, 1 H), 7.19-7.23 (m, 3 H), 7.33-7.39 (m, 3 H), 7.48-7.51 (m, 1 H), 7.70-7.72 (m, 1 H), 7.86 (d, $J = 8.3$ Hz, 1 H), 8.22 (d, $J = 5.2$ Hz, 1 H), 8.52 (s, 1 H);
- 10 MS m/e 484 (MH^+).

Example 89

15

To a solution of Example 88 (30.5 mg, 0.06 mmol) in MeOH (1 mL) was added ammonia (2 M in MeOH, 1 mL). The reaction mixture was stirred at room

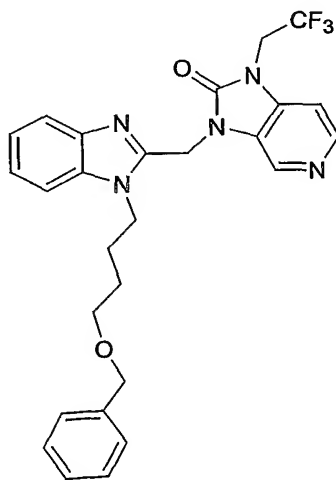
temperature for 16 hours. The solvent was concentrated. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) followed by treatment with excess 4 N HCl in dioxane gave Example 89 as the HCl salt.

5

¹H NMR (CD₃OD) δ 1.11-1.17 (m, 2 H), 1.21-1.26 (m, 2 H), 3.13-3.20 (m, 1 H), 3.59-3.66 (m, 2 H), 3.72-3.77 (m, 2 H), 5.98 (s, 2 H), 6.11 (s, 2 H), 7.62 (t, J = 7.4 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 4.2 Hz, 1 h), 8.04 (d, J = 8.0 Hz, 1 H), 8.58 (d, J = 3.9 Hz, 1 H), 8.89 (s, 1 H);

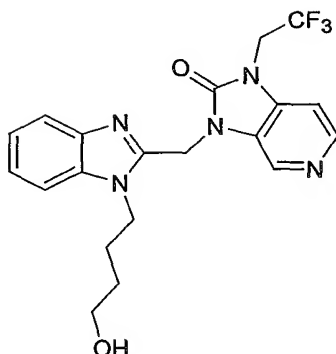
10 MS m/e 380 (MH⁺).

Example 90



15

MS m/e 510 (MH⁺).

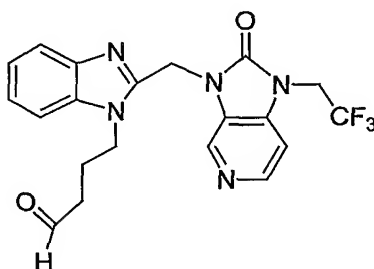
Example 91

5 Example 91 was prepared from Example 90 according to the same procedure described for Example 71.

^1H NMR (DMSO- d_6) δ 1.53-1.59 (m, 2 H), 1.87-1.92 (m, 2 H), 3.47 (t, J = 6.4 Hz, 2 H), 4.54 (t, J = 7.6 Hz, 2 H), 5.17 (q, J = 9.0 Hz, 2 H), 5.89 (s, 2 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.70 (d, J = 8.1 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 8.10 (d, J = 6.4 Hz, 1 H), 8.80 (d, J = 6.5 Hz, 1 H), 9.11 (s, 1 H).
10 MS m/e 420 (MH^+).

Example 92

15



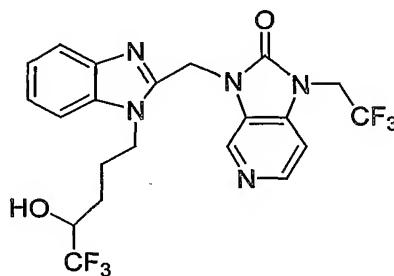
 Example 92 was prepared from Example 91 according to the same procedure described for Example 86.

20

^1H NMR (CDCl_3) δ 1.94-1.99 (m, 2 H), 2.59 (t, J = 6.7 Hz, 2 H), 4.31-4.35 (m, 2 H), 4.53 (q, J = 8.5 Hz, 2 H), 5.46 (s, 2 H), 7.07 (d, J = 6.4 Hz, 1 H), 7.27-7.34 (m,

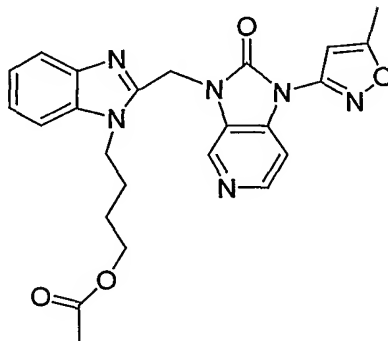
2 H), 7.44 (d, $J = 7.5$ Hz, 1 H), 8.78 (dd, $J = 0.9, 7.2$ Hz, 1 H), 8.39 (d, $J = 5.4$ Hz, 1 H), 8.85 (s, 1 H), 9.78 (s, 1 H);
MS m/e 418 (MH^+).

5

Example 93

Example 93 was prepared from Example 92 according to the same
10 procedure described for Example 87.

1H NMR (CD_3OD) δ 1.60-1.73 (m, 1 H), 1.78-1.90 (m, 1 H), 2.00-2.14 (m, 2 H),
3.96-4.01 (m, 1 H), 4.53 (t, $J = 7.8$ Hz, 2 H), 4.94 (q, $J = 8.9$ Hz, 2 H), 5.69 (s, 2 H),
7.34-7.44 (m, 2 H), 7.60 (d, $J = 7.8$ Hz, 1 H), 7.68 (d, $J = 7.5$ Hz, 1 H), 7.92 (d, $J =$
15 6.3 Hz, 1 H), 8.60 (d, $J = 5.7$ Hz, 1 H), 8.82 (s, 1 H);
MS m/e 488 (MH^+).

Example 94

20

^1H NMR (CDCl_3) δ 1.68-1.73 (m, 2 H), 1.74-1.80 (m, 2 H), 1.99 (s, 3 H), 2.54 (s, 3 H), 4.04 (t, $J = 6.3$ Hz, 2 H), 4.35 (t, $J = 7.5$ Hz, 2 H), 5.48 (s, 2 H), 6.97 (s, 1 H), 7.27-7.35 (m, 3 H), 7.78-7.80 (m, 1 H), 8.00 (d, $J = 5.4$ Hz, 1 H), 8.46 (d, $J = 5.4$ Hz, 1 H), 8.86 (s, 1 H);

5 IR (KBr, cm^{-1}) 3421, 1727, 1599, 1527, 1484, 1457, 1257, 751;

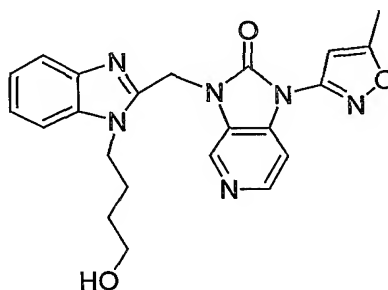
MS m/e 461 (MH^+);

Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_6\text{O}_4 \cdot 2.0 \text{ H}_2\text{O}$: C, 58.06; H, 5.68; N, 16.93

Found: C, 58.36; H, 5.55; N, 16.97.

10

Example 95



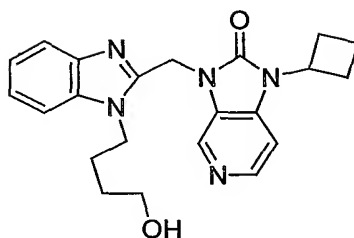
15 Example 95 was prepared from Example 94 according to the same procedure described for Example 73.

^1H NMR (CDCl_3) δ 1.60-1.66 (m, 2 H), 1.79-1.85 (m, 2 H), 3.65 (t, $J = 6.1$ Hz, 2 H), 4.35 (t, $J = 7.9$ Hz, 2 H), 5.50 (s, 2 H), 6.95 (s, 1 H), 7.28-7.36 (m, 3 H), 7.77-7.79 (m, 1 H), 8.00 (d, $J = 5.4$ Hz, 1 H), 8.45 (d, $J = 5.4$ Hz, 1 H), 8.87 (s, 1 H);

20 IR (KBr, cm^{-1}) 3309, 1728, 1602, 1528, 1483, 1452, 1385, 1171, 827, 739;

MS m/e 419 (MH^+).

Example 96

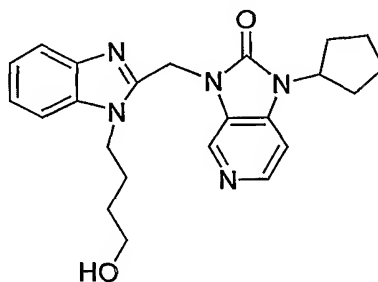


5 Example **96** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately by deprotection of the alcohol according to the same procedure described for Example **73**.

10 ¹H NMR (CDCl₃) δ 1.61-1.67 (m, 2 H), 1.79-1.85 (m, 2 H), 1.90-2.05 (m, 2 H), 2.43-2.49 (m, 2 H), 2.81-2.89 (m, 2 H), 3.68 (t, J=6.0 Hz, 2 H), 4.34 (t, J=7.8 Hz, 2 H), 4.85-4.92 (m, 1 H), 5.43 (s, 2 H), 7.22-7.35 (m, 4 H), 7.75-7.77 (m, 1 H), 8.33 (d, J= 5.5 Hz, 1 H), 8.82 (s, 1 H); MS m/e 392 (MH⁺);

15 Anal. Calcd for C₂₂H₂₅N₅O₂•0.5 H₂O: C, 65.98; H, 6.54; N, 17.49
 Found: C, 65.71; H, 6.62; N, 17.37.

Example 97



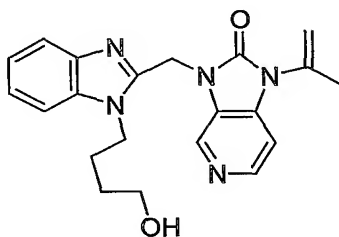
20

Example **97** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately

by deprotection of the alcohol according to the same procedure described for Example 73.

- ¹H NMR (CDCl₃) δ 1.61-1.67 (m, 2 H), 1.75-1.83 (m, 4 H), 1.95-2.02 (m, 2 H),
5 2.05-2.11 (m, 4 H), 3.68 (t, J = 6.0 Hz, 2 H), 4.35 (t, J = 7.9 Hz, 2 H), 4.82-4.89
(m, 1 H), 5.43 (s, 2 H), 7.04 (d, J = 5.5 Hz, 1 H), 7.22-7.30 (m, 2 H), 7.32-7.35
(m, 1 H), 7.76-7.78 (m, 1 H), 8.30 (d, J = 5.5 Hz, 1 H), 8.82 (s, 1 H);
IR (KBr, cm⁻¹) 3272, 2945, 2870, 1710, 1607, 1496, 1395, 742;
MS m/e 406 (MH⁺);
10 Anal. Calcd for C₂₃H₂₈N₅O₂: C, 67.95; H, 6.94; N, 17.22
Found: C, 67.78; H, 6.72; N, 16.92.

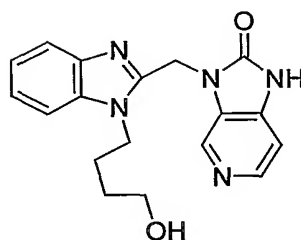
Example 98



15

Example 98 was prepared via synthesis of the acetate intermediate according to the same procedure described for Example 72 followed immediately by deprotection of the alcohol according to the same procedure described for
20 Example 73.

- ¹H NMR (DMSO-d₆) δ 1.43-1.48 (m, 2 H), 1.66-1.69 (m, 2 H), 2.18 (s, 3 H),
3.37-3.41 (m, 2 H), 4.35 (t, J = 7.3 Hz, 2 H), 4.47 (t, J = 5.1 Hz, 1 H), 5.25 (s, 1
H), 5.44 (s, 2 H), 5.46 (d, J = 1.0 Hz, 1 H), 7.17-7.27 (m, 3 H), 7.57-7.60 (m, 2 H),
25 8.25 (d, J = 5.2 Hz, 1 H), 8.48 (s, 1 H);
MS m/e 378 (MH⁺).

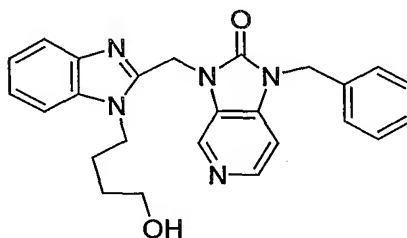
Example 99

5 Example 99 was prepared from Example 98 according to the same procedure described for Example 17.

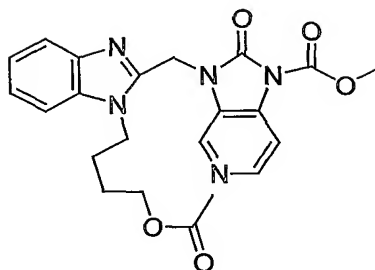
^1H NMR (DMSO- d_6) δ 1.44-1.48 (m, 2 H), 1.65-1.68 (m, 2 H), 3.38-3.42 (m, 2 H), 4.34 (t, $J = 7.5$ Hz, 2 H), 4.47 (t, $J = 5.1$ Hz, 1H), 5.38 (s, 1 H), 7.07 (d, $J = 5.2$ Hz, 1 H), 7.19 (t, $J = 7.0$ Hz, 1 H), 7.23 (t, $J = 7.0$ Hz, 1 H), 7.57 (t, $J = 8.0$ Hz, 1 H), 8.15 (d, $J = 5.1$ Hz, 1 H), 8.34 (s, 1 H), 11.59 (s, 1 H);
10 MS m/e 338 (MH^+).

Example 100

15

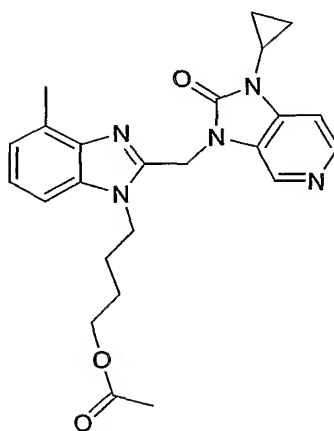


^1H NMR (CD_3OD) δ 1.54-1.60 (m, 2 H), 1.86-1.92 (m, 2 H), 3.52 (t, $J = 6.2$ Hz, 2 H), 4.45 (t, $J = 7.7$ Hz, 2 H), 5.20 (s, 1 H), 5.65 (d, $J = 6.8$ Hz, 2 H), 7.21-7.32 (m, 4 H), 7.34-7.37 (m, 3 H), 7.52-7.55 (m, 1 H), 7.63 (t, $J = 8.4$ Hz, 1 H), 8.37 (d, $J = 6.5$ Hz, 1 H), 8.68 (s, 1 H);
20 MS m/e 428 (MH^+).

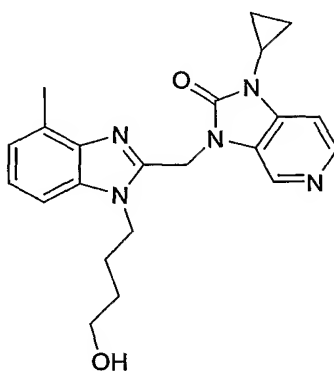
Example 101

5 To a solution of Example 99 (34 mg, 0.1 mmol) and 4-dimethylaminopyridine (DMAP, 2.0 mg, 0.02 mmol) in pyridine (1 ml) was added acetic anhydride (22 mg, 0.22 mmol) at room temperature. After stirring for 12 hours, the reaction mixture was diluted with EtOAc (10 ml) and washed twice with H₂O and brine. The combined organic extracts were dried over MgSO₄, and
10 concentrated. The residue was purified by flash column chromatography (CH₂Cl₂/MeOH, 20:1) to yield 35 mg (82%yield) of Example 101 as a white solid.

¹H NMR (CDCl₃) δ 1.69-1.82 (m, 4 H), 2.00 (s, 3 H), 2.80 (s, 3 H), 4.06 (t, J = 6.2 Hz, 2 H), 4.34 (t, J = 6.6 Hz, 2 H), 5.39 (s, 2 H), 7.26-7.32 (m, 3 H), 7.75-7.78 (m, 1 H), 8.03 (d, J = 5.1 Hz, 1 H), 8.42 (d, J = 3.2 Hz, 1 H), 8.82 (s, 1 H);
15 MS m/e 422 (MH⁺).

Example 102

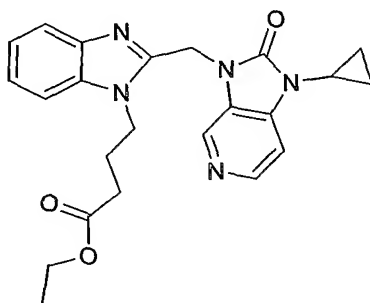
- 5 ^1H NMR (DMSO- d_6) δ 0.64-0.68 (m, 2 H), 0.81-0.86 (m, 2 H), 1.28-1.37 (m, 4 H), 1.72 (s, 3 H), 2.27 (s, 3 H), 2.73-2.77 (m, 1 H), 3.72 (t, $J = 6.2$ Hz, 2 H), 4.07 (t, $J = 7.1$ Hz, 2 H), 5.14 (s, 2 H), 6.76 (d, $J = 7.3$ Hz, 1 H), 6.90 (t, $J = 7.7$ Hz, 1 H), 7.03 (d, $J = 5.25$ Hz, 1 H), 7.13 (d, $J = 8.1$ Hz, 1 H), 8.00 (d, $J = 5.25$ Hz, 1 H), 8.23 (s, 1 H);
- 10 MS m/e 434 (MH^+).

Example 103

15

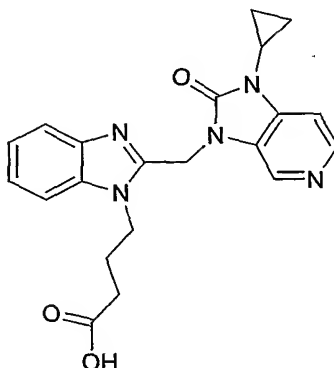
Example 103 was prepared from Example 102 according to the same procedure described for Example 73.

^1H NMR ($\text{DMSO}-d_6$) δ 0.90-0.95 (m, 2 H), 1.05-1.10 (m, 2 H), 1.35-1.41 (m, 2 H), 1.50-1.55 (m, 2 H), 2.51 (s, 3 H), 2.97-3.00 (m, 1 H), 4.27 (t, $J = 7.5$ Hz, 2 H), 4.43 (t, $J = 5.0$ Hz, 2 H), 5.38 (s, 2 H), 7.00 (d, $J = 7.2$ Hz, 1 H), 7.13 (t, $J = 7.7$ Hz, 1 H), 7.27 (d, $J = 5.2$ Hz, 1 H), 7.34 (d, $J = 8.1$ Hz, 1 H), 8.23 (d, $J = 5.2$ Hz, 1 H), 8.45 (s, 1 H);
MS m/e 392 (MH^+).

Example 104

10

^1H NMR (CDCl_3) δ 1.00-1.02 (m, 2 H), 1.14-1.18 (m, 2 H), 1.22 (t, $J = 7.1$ Hz, 3 H), 2.38 (t, $J = 7.15$ Hz, 2 H), 2.91-2.96 (m, 1 H), 4.10 (q, $J = 7.2$ Hz, 2 H), 4.38 (t, $J = 7.6$ Hz, 2 H), 5.37 (s, 2 H), 7.16 (d, $J = 5.4$ Hz, 1 H), 7.24-7.30 (m, 4 H), 7.39 (d, $J = 6.6$ Hz, 1 H), 7.75 (d, $J = 7.0$ Hz, 1 H), 8.33 (d, $J = 5.3$ Hz, 1 H), 8.71 (s, 1 H);
MS m/e 419 (MH^+).

Example 105

20

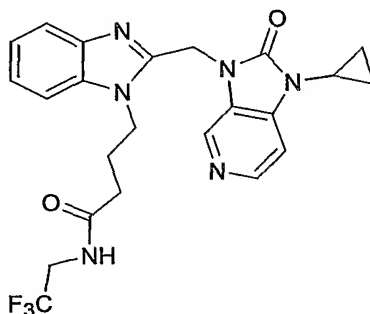
A mixture of Example **104** (346 mg, 0.83 mmol) and aqueous sodium hydroxide (1N, 4.1 mL, 4.13 mmol) were stirred in MeOH (5 mL) for 14 hours at room temperature. The mixture was neutralized with HCl followed by flash column chromatography to give Example **105**.

5

¹H NMR (CDCl₃) δ 1.13-1.16 (m, 2 H), 1.22-1.25 (m, 2 H), 2.36-2.41 (m, 4 H), 3.09-3.12 (m, 1 H), 4.56 (t, J = 6.6 Hz, 2 H), 5.91 (s, 2 H), 7.47-7.57 (m, 4 H), 7.93 (d, J = 7.6 Hz, 1 H), 8.37 (d, J = 6.4 Hz, 1 H), 9.17 (s, 1 H); MS m/e 392 (MH⁺).

10

Example 106

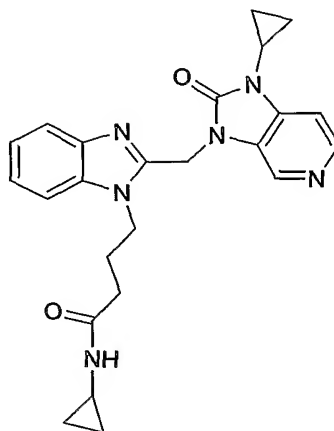


15 A solution of Example **105** (0.23 g, 0.50 mmol), 1-hydroxybenzotriazole
hydrate (HOBt, 75 mg, 0.54 mmol), trifluoroethylamine hydrochloride (75 mg,
0.54 mmol), and N-methylmorpholine (0.21 g, 2.16 mmol) was stirred at room
temperature for 30 minutes until a homogeneous solution resulted. 1-[3-
(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC ,103 mg,
20 0.54 mmol) was added and the mixture was stirred for 12 hours. The solution was
concentrated and the residue dissolved in EtOAc and washed with water and
saturated NaHCO₃, dried over MgSO₄ and concentrated to give 35 mg (18%
yield) of Example **106** as a white solid.

25 ¹H NMR (DMSO-d₆) δ 0.89-0.93 (m, 2 H), 1.06-1.08 (m, 2 H), 1.86-1.89 (m, 2 H), 2.27-2.30 (m, 2 H), 2.98-3.00 (m, 1 H), 4.31-4.34 (m, 2 H), 5.40 (s, 2 H),

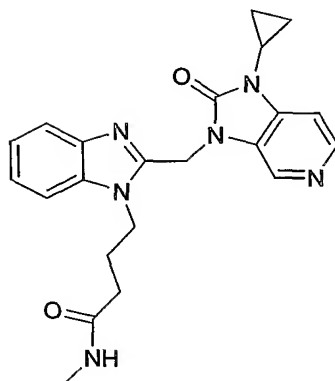
7.18-7.23 (m, 1 H), 7.25-7.29 (m, 2 H), 7.57-7.58 (m, 2 H) 8.25-8.26 (m, 1 H)
8.41 (s, 1 H), 8.57-8.60 (m, 1 H);
MS m/e 472 (MH⁺).

5

Example 107

Example 104 (100 mg, 0.24 mmol) in neat cyclopropylamine (1.22 g,
10 21.40 mmol) was heated at 105 °C in a sealed tube for 18 hours. The reaction
mixture was concentrated and the residue was purified by flash column
chromatography to give Example 107.

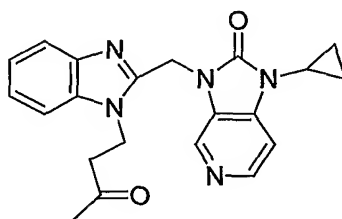
¹H NMR (CDCl₃) δ 0.45-0.48 (m, 2 H), 0.74-0.78 (m, 2 H), 0.98-1.03 (m, 2 H),
15 1.14-1.18 (m, 2 H), 1.99-2.04 (m, 2 H), 2.20 (t, J = 6.9 Hz, 2 H), 2.67-2.70 (m, 1
H), 2.92-2.96 (m, 1 H), 4.37 (t, J = 7.6 Hz, 2 H), 5.36 (s, 2 H), 7.14 (d, J = 5.2 Hz,
1 H), 7.24-7.29 (m, 2 H), 7.44 (d, J = 7.0 Hz, 1 H), 7.75 (d, J = 7.4 Hz, 1 H), 8.34
(d, J = 5.2 Hz, 1 H), 8.70 (s, 1 H);
MS m/e 431 (MH⁺).

Example 108

5 **Example 104** (52 mg, 0.12 mmol) in methylamine (40% aqueous solution, 4 mL) was heated at 120 °C in a sealed tube for 18 hours. The solvent was evaporated and the residue purified by flash column chromatography to give **Example 108** as a 2:1 mixture of cis/trans rotomers.

10 ^1H NMR (CDCl_3) δ 0.96-1.00 (m, 2 H), 1.08-1.14 (m, 2 H), 1.94-2.02 (m, 2 H), 2.19-2.23 (m, 2 H), 2.75 (d, $J = 6.0$ Hz, 3 H), 2.88-2.92 (m, 1 H), 4.29-4.36 (m, 2 H), 5.33, 5.34 (s, 2 H), 7.07, 7.10 (d, $J = 6.5$ Hz, 1 H), 7.11-7.27 (m, 2 H), 7.66-7.71 (m, 1 H), 8.25, 8.28 (d, $J = 6.7$ Hz, 1 H), 8.57, 8.63 (s, 1 H);
MS m/e 405 (MH^+).

15

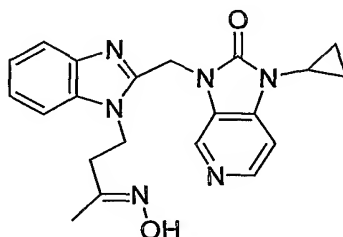
Example 109

20 A mixture of **Example 47** (500 mg, 1.64 mmol) and methyl vinyl ketone (574 mg, 8.2 mmol) in EtOH (10 ml) was heated to reflux for 8 hours. After

cooling, the solid was collected by filtration to give 378 mg (61%) of Example 109 as a white solid.

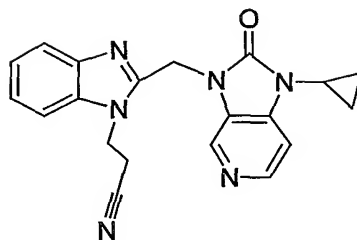
¹H NMR (CDCl₃) δ 1.01-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 2.10 (s, 3 H), 2.91-2.96 (m, 3 H), 4.60 (t, J=6.4 Hz, 2 H), 5.53 (s, 2 H), 7.17 (d, J=5.4 Hz, 1 H), 7.24-7.30 (m, 2 H), 7.32-7.34 (m, 1 H), 7.73-7.75 (m, 1 H), 8.34 (d, J=5.4 Hz, 1 H), 8.69 (s, 1 H);
MS m/e 376 (MH⁺).

10

Example 110

A mixture of Example 109 (37 mg, 0.10 mmol) and hydroxylamine hydrochloride (7.6 mg, 0.11 mmol) in MeOH (2 ml) was heated to reflux for 2 hours, diluted with EtOAc (20 ml) and washed with aqueous saturated NaHCO₃. The organic layer was separated, dried over MgSO₄, and evaporated to give 34 mg (87% yield) of Example 110 as white solid.

¹H NMR (CDCl₃) δ 1.01-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 1.89 (s, 3 H), 2.64 (t, J=6.5 Hz, 2 H), 2.89-2.92 (m, 1 H), 4.58 (t, J=6.6 Hz, 2 H), 5.41 (s, 2 H), 7.12-7.31 (m, 4 H), 7.69-7.72 (m, 1 H), 8.29 (d, J= 4.8 Hz, 1 H), 8.57 (s, 1 H);
MS m/e 391 (MH⁺).

Example 111

5 ^1H NMR (CDCl_3) δ 1.03-1.07 (m, 2 H), 1.16-1.20 (m, 2 H), 2.86 (t, $J = 6.5$ Hz, 2 H), 2.93-2.97 (m, 1 H), 4.78 (t, $J = 6.5$ Hz, 2 H), 5.43 (s, 2 H), 7.18 (d, $J = 5.4$ Hz, 1 H), 7.30-7.36 (m, 3 H), 7.81-7.82 (m, 1 H), 8.36 (d, $J = 5.4$ Hz, 1 H), 8.84 (s, 1 H);

IR (KBr, cm^{-1}) 3405, 1709, 1605, 1500, 1466, 1455, 1411, 1179, 750;

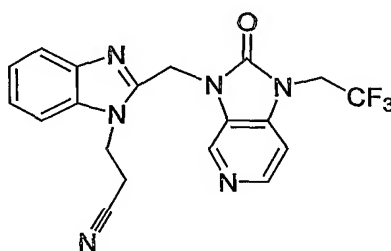
10 MS m/e 359 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_6\text{O} \cdot 0.5\text{H}_2\text{O}$: C, 65.38; H, 5.21; N, 22.87

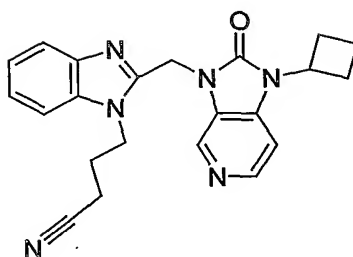
Found: C, 65.49; H, 5.09; N, 22.41.

Example 112

15



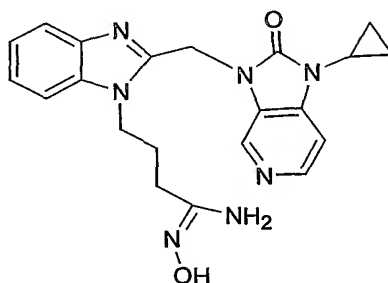
^1H NMR (CD_3OD) δ 3.11 (t, $J = 6.6$ Hz, 2 H), 4.72-4.82 (m, 4 H), 5.59 (s, 2 H), 7.28-7.38 (m, 3 H), 7.60-7.64 (m, 2 H), 8.29 (d, $J = 5.7$ Hz, 1 H), 8.53 (s, 1 H).

Example 113

5 ^1H NMR (CDCl_3) δ 1.90-2.10 (m, 4 H), 2.43-2.49 (m, 4 H), 2.80-2.89 (m, 2 H), 4.48 (t, $J=7.4$ Hz, 2 H), 4.84-4.90 (m, 1 H), 5.40 (s, 2 H), 7.21-7.38 (m, 4 H), 7.77-7.79 (m, 1 H), 8.34 (d, $J=5.5$ Hz, 1 H), 8.82 (s, 1 H); MS m/e 387 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}$: C, 68.37; H, 5.73; N, 21.74

10 Found: C, 68.21; H, 5.83; N, 21.71.

Example 114

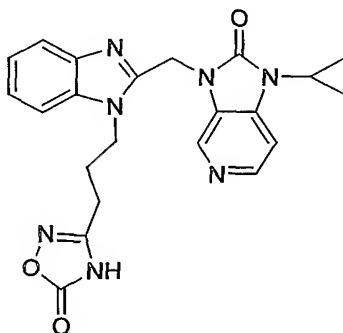
15

A mixture of Example 26 (610 mg, 1.62 mmol), hydroxylamine hydrochloride (408 mg, 5.87 mmol) and potassium carbonate (450 mg, 3.24 mmol) were stirred in a EtOH and H_2O (2:1 ratio mixture, 60 mL) at 80 °C for 18 hours. The solvent was evaporated and the residue was diluted with H_2O to dissolve inorganic salts. The white solid was filtered and dried under high vacuum to give 545 mg (83% yield) of Example 114 as a white solid.

20

¹H NMR (DMSO-d₆) δ 0.90-0.93 (m, 2 H), 1.05-1.07 (m, 2 H), 1.87-1.90 (m, 2 H), 2.06 (t, J = 7.5 Hz, 2 H), 3.00-3.02 (m, 1 H), 4.32 (t, J = 7.6 Hz, 2 H), 5.41 (s, 2 H), 5.46 (bs, 2 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.24 (t, J = 7.3 Hz, 1 H), 7.29 (d, J = 5.2 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.40 (s, 1 H), 8.84 (s, 1 H).

Example 115



10

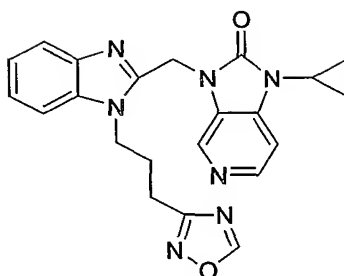
Example 114 (210 mg, 0.52 mmol) was treated with phosgene (20% in toluene, 2.56 g, 5.2 mmol) and heated to reflux for 12 hours. Additional phosgene (20% in toluene 2.56 g, 5.2 mmol) was added and the mixture heated to reflux for another 6 hours. The solution was concentrated to half volume and the white solid was isolated by filtration to give 138 mg (62% yield) of Example 115.

15

¹H NMR (DMSO-d₆) δ 1.05-1.05 (bs, 2 H), 1.15-1.16 (m, 2 H), 2.21-2.26 (m, 2 H), 2.71-2.75 (m, 2 H), 3.15-3.17 (m, 1 H), 4.51-4.58 (m, 2 H), 5.74-5.78 (m, 2 H), 7.37-7.40 (m, 1 H), 7.45-7.47 (m, 1 H), 7.63-7.66 (m, 1 H), 7.84-7.89 (m, 2 H), 8.64 (d, J = 6.4 Hz, 1 H), 8.92-8.95 (m, 1 H);
MS m/e 432 (MH⁺).

20

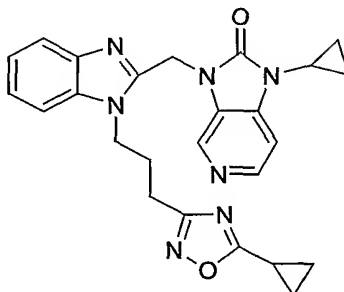
Example 116



5 A mixture of the Example **114** (100 mg, 0.24 mmol) was heated to reflux in triethylorthoformate (2.5 mL) for 12 hours. The solution was concentrated and the residue purified by preparative HPLC (C18, gradient 0-100% MeOH/H₂O with 0.1% trifluoroacetic acid). The product was treated with 4 N HCl in dioxane and concentrated to give 38 mg (35% yield) of the Example **116** as the
10 hydrochloride salt.

¹H NMR (DMSO-d₆) δ 0.97-1.02 (m, 2 H), 1.10-1.16 (m, 2 H), 2.25-2.35 (m, 2 H), 2.95-2.99 (m, 2 H), 3.14-3.16 (m, 1 H), 4.55-4.65 (m, 2 H), 5.77 (s, 2 H), 7.39-7.41 (m, 1 H), 7.46-7.48 (m, 1 H), 7.66-7.68 (m, 1 H), 7.84-7.90 (m, 2 H), 8.64 (d, J = 6.1 Hz, 1 H), 8.94 (s, 1 H), 9.57 (s, 1 H); MS m/e 416 (MH⁺).

Example 117



A mixture of Example 114 (250 mg, 0.62 mmol) was heated to reflux with cyclopropanecarbonyl chloride (354 mg, 3.39 mmol) and pyridine (2 mL) for 12

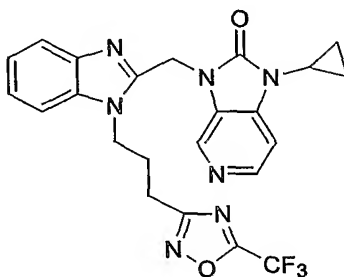
hours. The solution was concentrated and the residue purified by preparative HPLC (C18, gradient 0-100% MeOH/H₂O with 0.1% trifluoroacetic acid). The product was treated with 4N HCl in dioxane and concentrated to give 80 mg (28% yield) of Example 117 as the hydrochloride salt.

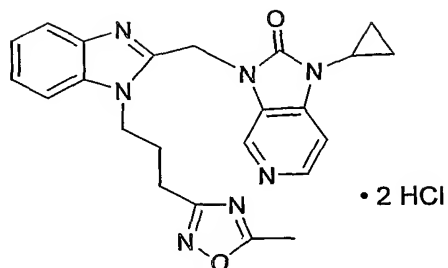
5

¹H NMR (DMSO-d₆) δ 1.04-1.06 (m, 4H), 1.13-1.15 (m, 2 H), 1.20-1.23 (m, 2 H), 2.21-2.31 (m, 2 H), 2.83-2.85 (m, 2 H), 3.11-3.19 (m, 1 H), 3.65-3.75 (m, 1 H), 4.55-4.57 (m, 2 H), 5.75 (s, 2 H), 7.35-7.42 (m, 1 H), 7.45-7.52 (m, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.83-7.85 (m, 2 H), 8.62 (d, J = 8.1 Hz, 1 H), 8.92 (s, 1 H);

10 MS m/e 456 (MH⁺).

Example 118



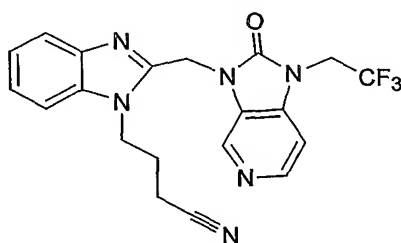
Example 119

5 Example 119 was prepared according to the same procedure described for Example 117 using acetic anhydride.

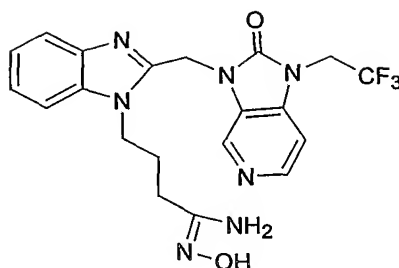
¹H NMR (DMSO-d₆) δ 1.01-1.05 (m, 2 H), 1.13-1.15 (m, 2 H), 2.24-2.28 (m, 2 H), 2.55 (s, 3 H), 2.85-2.88 (m, 1 H), 3.15-3.18 (m, 2 H), 4.55 (t, J = 7.4 Hz, 2 H),
10 5.71 (bs, 2 H), 7.29-7.38 (m, 1 H), 7.40-7.47 (m, 1 H), 7.64 (d, J = 7.4 Hz, 1 H), 7.80-7.86 (m, 2 H), 8.63 (d, J = 6.4 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 430 (MH⁺).

Example 120

15



¹H NMR (DMSO-d₆) δ 2.06-2.12 (m, 2 H), 2.63 (t, J = 7.3 Hz, 2 H), 4.42 (t, J = 7.5 Hz, 2 H), 4.92 (q, J = 9.3 Hz, 2 H), 5.51 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.27
20 (t, J = 7.5 Hz, 1 H), 7.45 (d, J = 5.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.62 (d, J = 8.2 Hz, 1 H), 8.33 (d, J = 5.5 Hz, 1 H), 8.51 (s, 1 H).

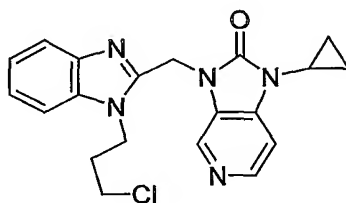
Example 121

5 Example 121 was prepared from Example 120 according to the same procedure as Example 114.

¹H NMR (DMSO-d₆) δ 1.91-1.98 (m, 2 H), 2.30 (t, J = 7.0 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 4.91 (q, J = 9.1 Hz, 2 H), 5.51 (s, 2 H), 7.15-7.18 (m, 1 H), 7.23-7.27 (m, 1 H), 7.44 (d, J = 5.2 Hz, 1 H), 7.55 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.06 (bs, 1 H), 8.31 (d, J = 5.2 Hz, 2 H), 8.46 (s, 1 H), 9.48 (s, 1 H);
 10 MS m/e 448 (MH⁺).

Example 122

15

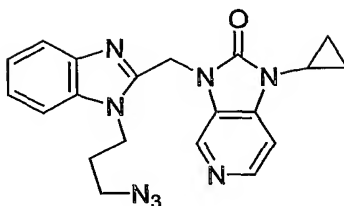


¹H NMR (CDCl₃) δ 1.00-1.06 (m, 2 H), 1.15-1.19 (m, 2 H), 2.14-2.19 (m, 2 H), 2.91-2.95 (m, 1 H), 3.55 (t, J=6.0 Hz, 2 H), 4.52 (t, J=6.7 Hz, 2 H), 5.40 (s, 2 H),
 20 7.14-7.15 (m, 1 H), 7.26-7.32 (m, 2 H), 7.39-7.40 (m, 1 H), 7.76-7.78 (m, 1 H), 8.34 (d, J=5.0 Hz, 1 H), 8.72 (s, 1 H);
 MS m/e 382 (MH⁺);

Anal. Calcd for C₂₀H₂₀ClN₅O: C, 62.90; H, 5.27; N, 18.34

Found: C, 62.58; H, 5.17; N, 18.18.

Example 123



5 A mixture of Example 122 (38 mg, 0.10 mmol) and sodium azide (20 mg, 0.30 mmol) in DMF (2 ml) was heated to 70 °C for 2 hours. The final solution was diluted with EtOAc (10 ml) and washed with H₂O (3 x 10 ml) and brine. The combined organic extracts were dried over MgSO₄, concentrated, and purified by flash chromatography, (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) to yield 33 mg
10 (85% yield) of Example 123 as a white solid.

¹H NMR (CDCl₃) δ 1.00-1.05 (m, 2 H), 1.13-1.19 (m, 2 H), 1.91-1.97 (m, 2 H), 2.90-2.94 (m, 1 H), 3.35 (t, J = 6.3 Hz, 2 H), 4.43 (t, J = 7.2 Hz, 2 H), 5.37 (s, 2 H), 7.12 (d, J = 5.2 Hz, 1 H), 7.26-7.30 (m, 2 H), 7.33-7.35 (m, 1 H), 7.77 (d, J =
15 7.2 Hz, 1 H), 8.32 (d, J = 5.0 Hz, 1 H), 8.72 (s, 1 H);

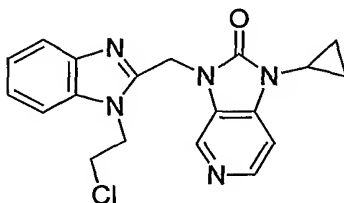
MS m/e 388 (MH⁺);

Anal. Calcd for C₂₀H₂₀N₈O: C, 61.84; H, 5.19; N, 28.84

Found: C, 61.59; H, 5.27; N, 28.50.

20

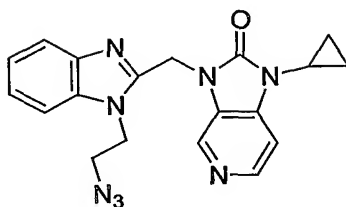
Example 124



¹H NMR (CDCl₃) δ 1.02-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 2.90-2.95 (m, 1 H),
25 3.77 (t, J = 6.0 Hz, 2 H), 4.76 (t, J = 6.1 Hz, 2 H), 5.44 (s, 2 H), 7.14 (d, J = 5.2

Hz, 1 H), 7.28-7.32 (m, 3 H), 7.78-7.80 (m, 1 H), 8.34 (d, $J = 4.8$ Hz, 1 H), 8.77 (s, 1 H);
MS m/e 368 (MH^+).

5

Example 125

Example 125 was prepared from Example 124 according to the same
10 procedure described for Example 123.

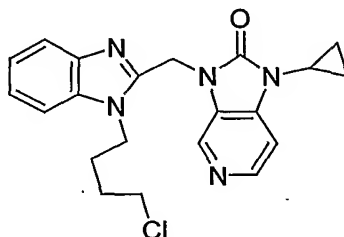
1H NMR ($CDCl_3$) δ 1.01-1.06 (m, 2 H), 1.16-1.20 (m, 2 H), 2.92-2.96 (m, 1 H),
3.70 (t, $J = 6.0$ Hz, 2 H), 4.54 (t, $J = 6.1$ Hz, 2 H), 5.43 (s, 2 H), 7.15 (d, $J = 5.2$
15 Hz, 1 H), 7.29-7.32 (m, 3 H), 7.78-7.81 (m, 1 H), 8.34 (d, $J = 4.8$ Hz, 1 H), 8.79
(s, 1 H);

MS m/e 375 (MH^+);

Anal. Calcd for $C_{19}H_{18}N_8O \cdot 0.25 H_2O$: C, 60.23; H, 4.92; N, 29.57

Found: C, 60.30; H, 4.85; N, 29.44.

20

Example 126

1H NMR ($CDCl_3$) δ 1.00-1.04 (m, 2 H), 1.16-1.20 (m, 2 H), 1.79-1.81 (m, 4 H),
25 2.92-2.96 (m, 1 H), 3.49-3.50 (m, 2 H), 4.35 (s, 2 H), 5.37 (s, 2 H), 7.13 (d, $J=5.2$

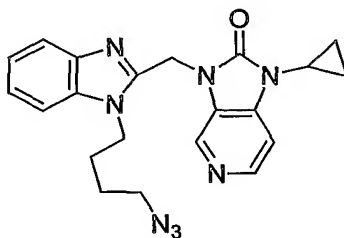
Hz, 1 H), 7.26-7.33 (m, 3 H), 7.76-7.79 (m, 1 H), 8.83 (d, J=5.2 Hz, 1 H), 8.72 (s, 1 H);

MS m/e 396 (MH⁺);

Anal. Calcd for C₂₁H₂₂ClN₅O • 0.20 H₂O: C, 63.14; H, 5.64; N, 17.53

Found: C, 62.74; H, 5.54; N, 17.57.

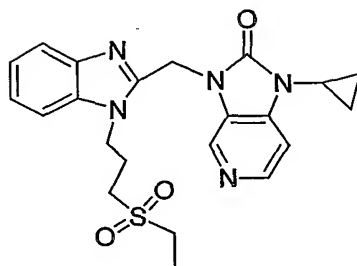
Example 127



Example 127 was prepared from Example 126 according to the same procedure described for Example 123.

¹H NMR (CDCl₃) δ 0.99-1.02 (m, 2 H), 1.15-1.19 (m, 2 H), 1.58-1.63 (m, 2 H), 1.69-1.75 (m, 2 H), 2.90-2.95 (m, 1 H), 3.27 (t, J = 6.5 Hz, 2 H), 4.32 (t, J = 7.3 Hz, 2 H), 5.35 (s, 2 H), 7.12 (d, J = 5.0 Hz, 1 H), 7.25-7.31 (m, 3 H), 7.76-7.77 (m, 1 H), 8.32 (d, J = 4.8 Hz, 1 H), 8.71 (s, 1 H);
MS m/e 403 (MH⁺).

Example 128



5 ^1H NMR (DMSO- d_6) δ 0.91-0.94 (m, 2 H), 1.04-1.09 (m, 2 H), 1.20 (t, J = 7.5 Hz, 3 H), 2.06-2.13 (m, 2 H), 2.98-3.02 (m, 1 H), 3.11 (q, J = 7.5 Hz, 2 H), 3.16-3.21 (m, 2 H), 4.86 (t, J = 7.6 Hz, 2 H), 5.42 (s, 2 H), 7.18-7.21 (m, 1 H), 7.26-7.30 (m, 2 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H), 8.26 (d, J = 5.3 Hz, 1 H), 8.44 (s, 1 H);

10 IR (KBr, cm^{-1}) 3421, 1610, 1706, 1500, 1458, 1409, 1298, 1131, 751;

MS m/e 440 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_3\text{S} \cdot 2 \text{H}_2\text{O}$:

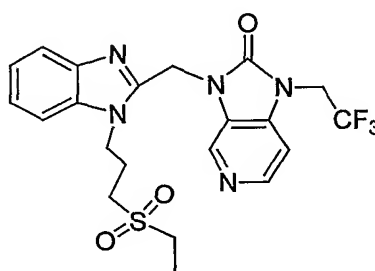
C, 55.56; H, 6.15; N, 14.73

Found:

C, 55.29; H, 5.89; N, 14.59.

15

Example 129



20 ^1H NMR (DMSO- d_6) δ 1.21 (t, J = 7.4 Hz, 3 H), 2.14-2.16 (m, 2 H), 3.13 (q, J = 7.4 Hz, 2 H), 3.22 (t, J = 7.5 Hz, 2 H), 4.50 (t, J = 7.5 Hz, 2 H), 4.91 (q, J = 9.3 Hz, 2 H), 5.53 (s, 2 H), 7.19 (t, J = 7.7 Hz, 1 H), 7.28 (t, J = 7.7 Hz, 1 H), 7.46 (d, J = 5.3 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 8.33 (d, J = 5.0 Hz, 1 H), 8.52 (s, 1 H);

IR (KBr, cm^{-1}) 3430, 2945, 1726, 1615, 1500, 1411, 1266, 1170, 1125, 745;

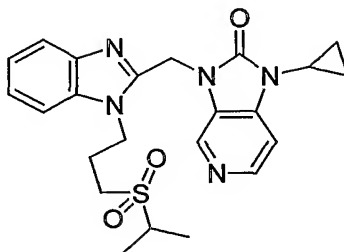
MS m/e 482 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_5\text{O}_3\text{S} \cdot 0.25 \text{H}_2\text{O}$: C, 51.90; H, 4.67; N, 14.41

Found: C, 51.69; H, 4.74; N, 14.17.

5

Example 130



10 ^1H NMR ($\text{DMSO}-d_6$) δ 0.92-0.93 (m, 2 H), 1.05-1.07 (m, 2 H), 1.23 (d, $J=6.8$ Hz, 6 H), 2.06-2.12 (m, 2 H), 2.98-3.02 (m, 1 H), 3.16-3.20 (m, 2 H), 3.28-3.30 (m, 1 H), 4.49 (t, $J=7.6$ Hz, 2 H), 5.42 (s, 2 H), 7.21 (t, $J=7.1$ Hz, 1 H), 7.26-7.30 (m, 2 H), 7.59 (d, $J=8.0$ Hz, 1 H), 7.64 (d, $J=8.0$ Hz, 1 H), 8.25 (d, $J=5.2$ Hz, 1 H), 8.44 (s, 1 H);

15 IR (KBr, cm^{-1}) 2926, 1720, 1604, 1498, 1471, 1420, 1267, 1126, 746;

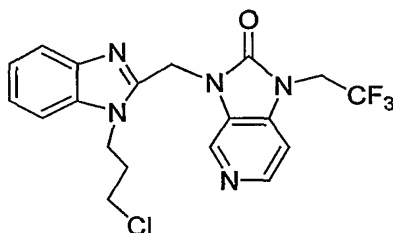
MS m/e 454 (MH^+);

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_3\text{S} \cdot 0.7 \text{H}_2\text{O}$: C, 59.26; H, 6.14; N, 15.02

Found: C, 59.58; H, 6.10; N, 14.63.

20

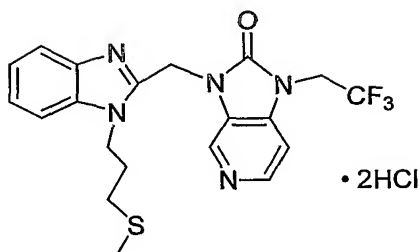
Example 131



25 ^1H NMR (CDCl_3) δ 2.03-2.17 (m, 2 H), 3.53 (t, $J=6.2$ Hz, 2 H), 4.45-4.54 (m, 4 H), 5.44 (s, 2 H), 7.01 (d, $J=5.1$ Hz, 1 H), 7.24-7.32 (m, 2 H), 7.37-7.41 (m, 2 H), 7.73-7.78 (m, 1 H), 8.36 (d, $J=5.4$ Hz, 1 H), 8.79 (s, 1 H);

MS m/e 424 (MH^+).

Example 132



5

To a volume of DMF (10 mL) saturated with excess methanethiol at -78 °C was added sodium hydride (60% suspension in mineral oil, 56 mg, 1.39 mmol). The mixture was warmed to 0 °C and stirred for 30 minutes. The mixture was then added to a solution of Example 131 (394 mg, 0.93 mmol) in DMF (2 mL) and was stirred at 0 °C for 30 minutes. The solvent was evaporated under high vacuum. The residue was neutralized with concentrated HCl and the solvent was evaporated. The residue was diluted with CH₂Cl₂ and was washed with saturated aqueous NaHCO₃ and H₂O, dried over MgSO₄, and evaporated.

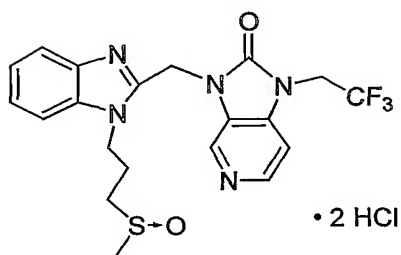
15 Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) gave 374 mg (93% yield) of Example 132. Example 132 (200 mg, 0.46 mmol) was converted to the HCl salt by treating a solution of Example 132 in MeOH with excess 4N HCl in dioxane and then by evaporating the solvent to give 223 mg (96% yield).

20

¹H NMR (CD₃OD) δ 2.14 (s, 3 H), 2.30-2.39 (m, 2 H), 2.70 (t, J = 6.6 Hz, 2 H), 4.78 (t, J = 7.4 Hz, 2 H), 5.01 (q, J = 8.7 Hz, 2 H), 6.05 (s, 2 H), 7.62-7.75 (m, 2 H), 7.76 (d, J = 7.5 Hz, 1 H), 7.99-8.04 (m, 2 H), 8.71 (d, J = 6.6 Hz, 1 H), 9.09 (s, 1 H);

25 IR (KBr, cm⁻¹) 3412, 2762, 1760, 1655, 1624, 1519, 1264, 1169, 1119, 834, 752;
MS m/e 436 (MH^+).

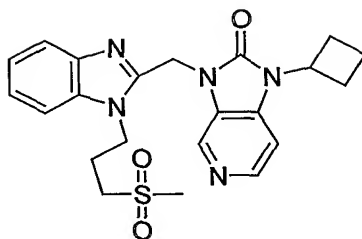
Example 133



5 A mixture of Example 132 (174 mg, 0.40 mmol) and sodium periodate (94 mg, 0.44 mmol) in H₂O (5 mL) was stirred at 0 °C. To this mixture was added DMF (2 mL) in order to dissolve the solids and the resulting solution was stirred at room temperature for 48 hours. The reaction mixture was diluted with CH₂Cl₂, washed with water, dried over MgSO₄ and evaporated. Purification by flash
10 column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) gave 145 mg (81% yield) of Example 133 which was converted to the HCl salt by treating a solution of Example 133 in MeOH with 4N HCl in dioxane and then by evaporating the solvent.

15 ¹H NMR (CD₃OD) δ 2.02-2.15 (m, 2 H), 2.53 (s, 3 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.43-4.56 (m, 4 H), 5.43 (s, 2 H), 7.02 (d, J = 5.1 Hz, 1 H), 7.26-7.31 (m, 2 H), 7.35-7.38 (m, 1 H), 7.74-7.77 (m, 1 H), 8.35 (d, J = 5.4 Hz, 1 H), 8.79 (s, 1 H); IR (KBr, cm⁻¹) 3412, 2854, 1760, 1656, 1624, 1519, 1264, 1169, 1120, 753; MS m/e 452 (MH⁺);

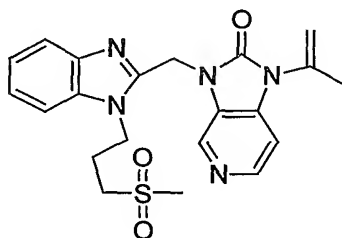
20	Anal. Calcd for $C_{20}H_{20}F_3N_5O_2S \cdot 2HCl \cdot H_2O$:	C, 44.29; H, 4.46; N, 12.91
	Found:	C, 44.08; H, 4.93; N, 11.54.

Example 135

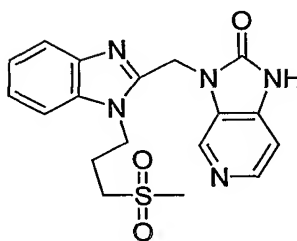
- 5 ^1H NMR (DMSO- d_6) δ 1.73-1.92 (m, 2 H), 2.13-2.16 (m, 2 H), 2.31-2.33 (m, 2 H), 2.79-2.83 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.7$ Hz, 2 H), 4.49 (t, $J = 7.4$ Hz, 2 H), 4.85-4.92 (m, 1 H), 5.44 (s, 2 H), 7.19-7.20 (m, 1 H), 7.26-7.27 (m, 1 H), 7.49 (d, $J = 5.3$ Hz, 1 H), 7.57 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.05$ Hz, 1 H), 8.25 (d, $J = 5.3$ Hz, 1 H), 8.46 (s, 1 H);
- 10 MS m/e 440 (MH^+);
- Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$: C, 60.11; H, 5.73; N, 15.93
- Found: C, 60.09; H, 5.76; N, 15.89.

Example 136

15



- ^1H NMR (DMSO- d_6) δ 2.12-2.18 (m, 5 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H), 4.51 (t, $J = 7.6$ Hz, 2 H), 5.45-5.48 (m, 3 H), 7.19-7.28 (m, 3 H), 7.59 (d, $J = 8.0$ Hz, 1 H), 7.64 (d, $J = 8.1$ Hz, 1 H), 8.26 (d, $J = 5.3$ Hz, 1 H), 8.52 (s, 1 H);
- 20 MS m/e 426 (MH^+).

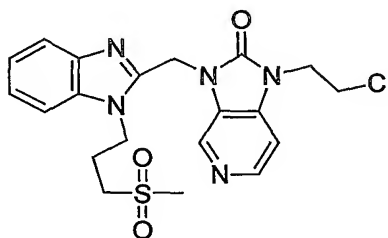
Example 137

5 Example 137 was prepared from Example 136 according to the same procedure described for Example 17.

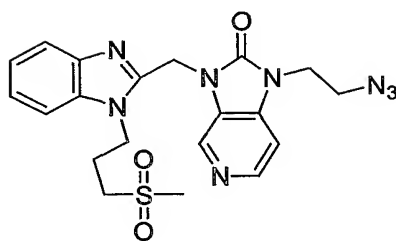
^1H NMR (DMSO-d_6) δ 2.12-2.16 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H),
4.49 (t, $J = 7.6$ Hz, 2 H), 5.41 (s, 2 H), 7.08 (d, $J = 7.0$ Hz, 1 H), 7.17-7.20 (m, 1
10 H), 7.25-7.29 (m, 1 H), 7.58 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 8.17
(d, $J = 5.2$ Hz, 1 H), 8.39 (s, 1 H);
MS m/e 386 (MH^+).

Example 138

15



^1H NMR (CDCl_3) δ 2.16-2.22 (m, 2 H), 2.91 (s, 3 H), 3.09 (t, $J = 7.3$ Hz, 2 H),
3.88 (t, $J = 5.9$ Hz, 2 H), 4.26 (t, $J = 6.0$ Hz, 2 H), 4.51 (t, $J = 7.6$ Hz, 2 H), 5.44 (s,
20 2 H), 7.20 (d, $J = 5.3$ Hz, 1 H), 7.28-7.34 (m, 2 H), 7.37-7.39 (m, 1 H), 7.78-7.80
(m, 1 H), 8.36 (d, $J = 5.1$ Hz, 1 H), 8.78 (s, 1 H);
MS m/e 448 (MH^+).

Example 139

5 Example 139 was prepared from Example 138 according to the same procedure described for Example 123.

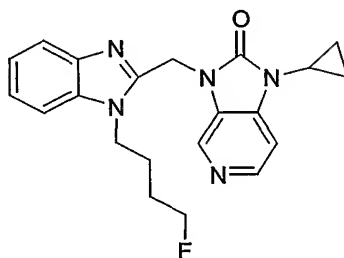
^1H NMR (CDCl_3) δ 2.18-2.24 (m, 2 H), 2.91 (s, 3 H), 3.09 (t, $J = 7.3$ Hz, 2 H),
3.73 (t, $J = 5.9$ Hz, 2 H), 4.08 (t, $J = 6.0$ Hz, 2 H), 4.51 (t, $J = 7.6$ Hz, 2 H), 5.44 (s,
10 2 H), 7.07 (d, $J = 5.3$ Hz, 1 H), 7.26-7.33 (m, 2 H), 7.33-7.38 (m, 1 H), 7.77-7.79
(m, 1 H), 8.36 (d, $J = 5.1$ Hz, 1 H), 8.79 (s, 1 H);

MS m/e 455 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_3\text{S} \cdot 0.5 \text{H}_2\text{O}$: C, 51.83; H, 5.00; N, 24.17

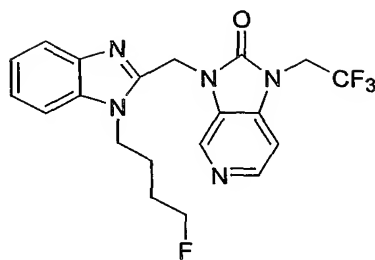
Found: C, 51.85; H, 4.82; N, 23.97.

15

Example 140

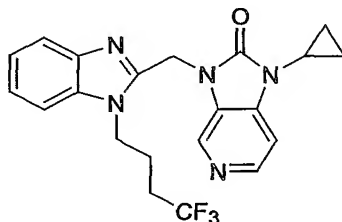
20 ^1H NMR ($\text{DMSO}-d_6$) δ 0.89-0.92 (m, 1 H), 1.06-1.08 (m, 1 H), 1.65-1.72 (m, 2
H), 2.96-2.99 (m, 1 H), 4.35-4.50 (m, 3 H), 5.40 (s, 2 H), 7.17-7.20 (m, 1 H),
7.24-7.29 (m, 2 H), 7.59 (d, $J = 8.2$ Hz, 2 H), 8.25 (d, $J = 5.1$ Hz, 1 H), 8.41 (s, 1
H);

MS m/e 380 (MH^+).

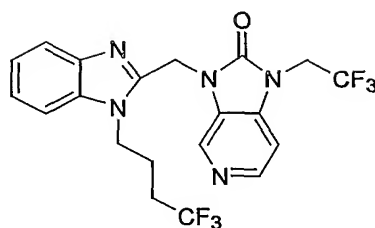
Example 141

- 5 ^1H NMR (DMSO- d_6) δ 1.67-1.77 (m, 4 H), 4.37-4.42 (m, 3 H), 4.49-4.51 (m, 1 H), 4.92 (q, $J = 9.2$ Hz, 2 H), 5.50 (s, 2 H), 7.18 (t, $J = 7.6$ Hz, 1 H), 7.26 (t, $J = 7.7$, 1 H), 7.44 (d, $J = 4.3$, 1 H), 7.57-7.61 (m, 2 H), 8.30-8.33 (bs, 1 H), 8.49-8.51 (bs, 1 H);
MS m/e 422 (MH^+).

10

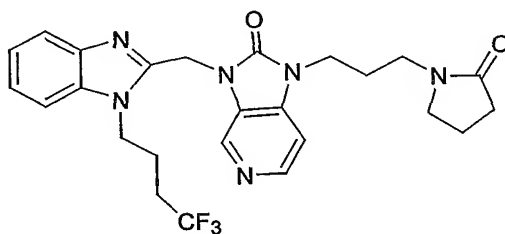
Example 142

- 15 ^1H NMR (DMSO- d_6) δ 1.03-1.04 (m, 2 H), 1.14-1.16 (m, 2 H), 2.06-2.08 (m, 2 H), 3.11-3.18 (m, 1 H), 4.52-4.55 (m, 4 H), 5.70 (s, 2 H), 7.34-7.39 (m, 1 H), 7.43-7.47 (m, 1 H), 7.63 (d, $J = 8.1$ Hz, 1 H), 7.84 (d, $J = 6.4$ Hz, 2 H), 8.63 (d, $J = 6.4$ Hz, 1 H), 8.92 (s, 1 H);
MS m/e 416 (MH^+).

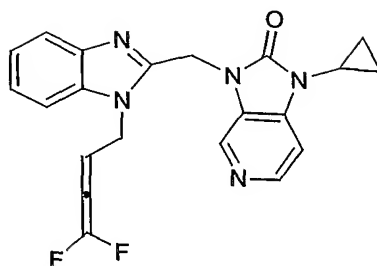
Example 143

- 5 ^1H NMR (DMSO- d_6) δ 1.84-1.87 (m, 2 H), 4.50-4.53 (m, 4 H), 5.14 (q, J = 9.0 Hz, 2 H), 5.74 (s, 2 H), 7.30-7.32 (m, 1 H), 7.37-7.40 (m, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 8.0, 1 H), 8.05 (d, J = 6.2 Hz, 1 H), 8.74 (d, J = 6.3 Hz, 1 H), 9.04 (s, 1 H);
MS m/e 458 (MH^+).

10

Example 144

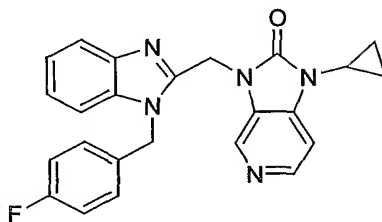
- 15 ^1H NMR (DMSO- d_6) δ 1.85-1.92 (m, 6 H), 2.18 (t, J = 8.1 Hz, 2 H), 2.36-2.41 (m, 2 H), 2.34 (t, J = 7.3 Hz, 2 H), 3.88 (t, J = 7.3 Hz, 2 H), 4.43 (t, J = 7.6 Hz, 2 H), 5.46 (s, 2 H), 7.19 (t, J = 7.0 Hz, 1 H), 7.27 (t, J = 7.0 Hz, 1 H), 7.38 (d, J = 5.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 1 H), 8.26 (d, J = 5.2 Hz, 1 H), 8.46 (s, 1 H);
20 MS m/e 501 (MH^+).

Example 145

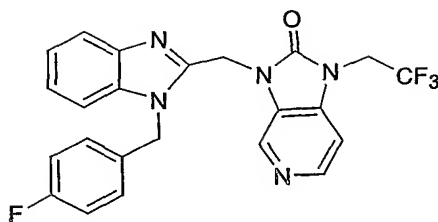
5 **Example 145** was prepared according to the general coupling procedure described in Scheme I-C with 4-bromo-1,1,2-trifluoro-1-butene which gave an elimination product.

¹H NMR (DMSO-d₆) δ 0.96-0.99 (m, 2 H), 1.14-1.16 (m, 2 H), 3.15-3.17 (m, 1
10 H), 5.53 (s, 2 H), 5.72 (d, J = 11.6 Hz, 1 H), 5.81 (d, J = 17.4 Hz, 1 H), 6.77-6.86 (m, 1 H), 7.34-7.42 (m, 2 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H), 7.85 (d, J = 6.4 Hz, 1 H), 8.64 (d, J = 6.1 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 394 (MH⁺).

15

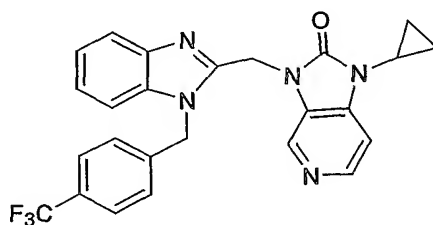
Example 146

¹H NMR (DMSO-d₆) δ 0.64-0.66 (m, 2 H), 0.97-0.98 (m, 2 H), 2.77-2.78 (m, 1 H),
20 5.40 (s, 2 H), 5.59 (s, 2 H), 6.77-6.81 (m, 2 H), 6.94 (t, J = 8.9 Hz, 2 H), 7.15 (d, J = 5.2 Hz, 1 H), 7.21-7.23 (m, 2 H), 7.40-7.42 (m, 1 H), 7.68-7.70 (m, 1 H), 8.20 (d, J = 5.2 Hz, 1 H), 8.31 (s, 1 H); MS m/e 413 (MH⁺).

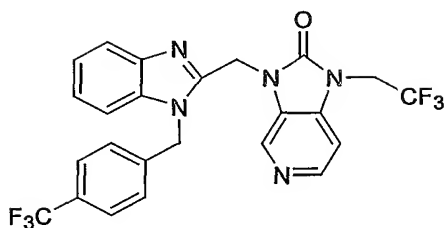
Example 147

- 5 ^1H NMR (DMSO- d_6) δ 4.74-4.79 (m, 2 H), 5.49 (s, 2 H), 5.60 (s, 2 H), 6.96-7.04 (m, 4 H), 7.17-7.25 (m, 2 H), 7.36 (d, $J = 5.2$ Hz, 1 H), 7.48 (d, $J = 7.3$ Hz, 1 H), 7.65 (d, $J = 6.7$ Hz, 1 H), 8.28 (d, $J = 5.5$ Hz, 1 H), 8.36 (s, 1 H);
MS m/e 456 (MH^+).

10

Example 148

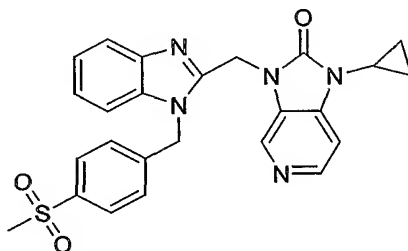
- 15 ^1H NMR (DMSO- d_6) δ 0.53-0.56 (m, 2 H), 0.92-0.96 (m, 2 H), 2.66-2.69 (m, 1 H), 5.41 (s, 2 H), 5.71 (s, 2 H), 6.83 (d, $J = 8.2$ Hz, 2 H), 7.06 (d, $J = 5.2$ Hz, 1 H), 7.23-7.25 (m, 2 H), 7.40-7.42 (m, 3 H), 7.72-7.74 (m, 1 H), 8.18 (d, $J = 5.1$ Hz, 1 H), 8.30 (s, 1 H);
MS m/e 464 (MH^+).

Example 149

- 5 ^1H NMR (DMSO- d_6) δ 4.68-4.70 (m, 2 H), 5.49 (s, 2 H), 5.74 (s, 2 H), 7.04 (d, J = 8.1 Hz, 2 H), 7.22-7.23 (m, 2H), 7.31 (d, J = 5.3 Hz, 1 H), 7.40-7.50 (m, 1H), 7.51 (d, J = 8.2 Hz, 2 H), 7.64-7.70 (m, 1 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.38 (s, 1 H);

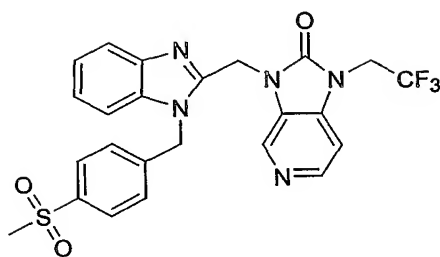
MS m/e 464 (MH^+).

10

Example 150

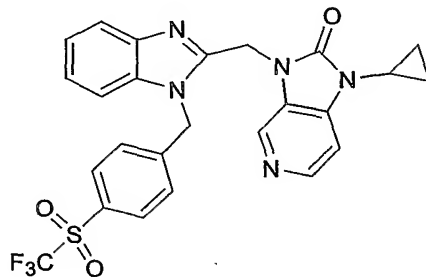
- 15 ^1H NMR (DMSO- d_6) δ 0.76-0.77 (m, 2 H), 1.05-1.07 (m, 2 H), 2.92-2.96 (m, 1 H), 3.56 (s, 3 H), 5.56 (s, 2 H), 5.81 (s, 2 H), 7.14 (d, J = 8.3 Hz, 2 H), 7.26-7.28 (m, 2 H), 7.47-7.49 (m, 1 H), 7.68-7.71 (m, 2 H), 7.77 (d, J = 8.4 Hz, 2 H), 8.58 (d, J = 6.4 Hz, 1 H), 8.72 (s, 1 H);

MS m/e 474 (MH^+).

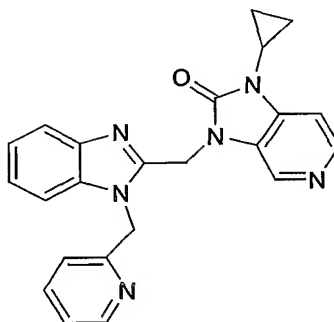
Example 151

- 5 ^1H NMR (DMSO- d_6) δ 3.20 (s, 3 H), 4.95-5.02 (m, 2 H), 5.66 (s, 2 H), 5.84 (s, 2 H), 5.56 (s, 2 H), 5.81 (s, 2 H), 7.26-7.29 (m, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 7.51-7.53 (m, 1 H), 7.64-7.66 (m, 1 H), 7.85 (d, J = 8.4 Hz, 2 H), 7.99 (d, J = 6.3 Hz, 1 H), 8.71 (d, J = 6.4 Hz, 1 H), 8.93 (s, 1 H);
MS m/e 516 (MH^+).

10

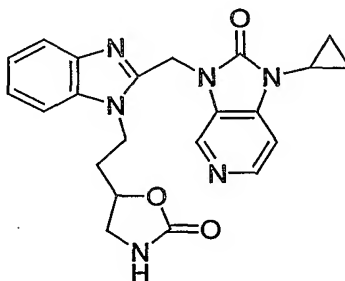
Example 152

- 15 ^1H NMR (DMSO- d_6) δ 0.78-0.81 (m, 2 H), 1.05-1.09 (m, 2 H), 2.95-2.98 (m, 1 H), 5.60 (s, 2 H), 5.95 (s, 2 H), 7.30 (dd, J = 3.0, 6.1 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.48-7.51 (m, 2 H), 7.71 (dd, J = 3.0, 6.1 Hz, 2 H), 7.73 (d, J = 6.4 Hz, 1 H), 8.04 (d, J = 8.6 Hz, 1 H), 8.60 (d, J = 6.4 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 528 (MH^+).

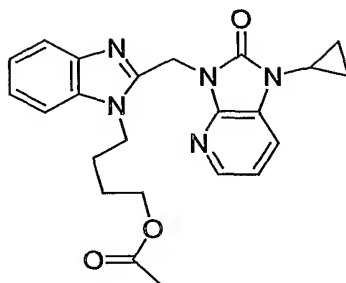
Example 153

- 5 ^1H NMR (DMSO-d_6) δ 0.68-0.71 (m, 2 H), 0.96-1.00 (m, 2 H), 2.79-2.82 (m, 1 H), 5.49 (s, 2 H), 5.69 (s, 2 H), 7.02 (d, $J = 7.9$ Hz, 1 H), 7.16-7.21 (m, 4 H), 7.43-7.45 (m, 1 H), 7.59-7.65 (m, 2 H), 8.21 (d, $J = 5.0$ Hz, 1 H), 8.24 (d, $J = 3.9$ Hz, 1 H), 8.35 (s, 1 H);

10

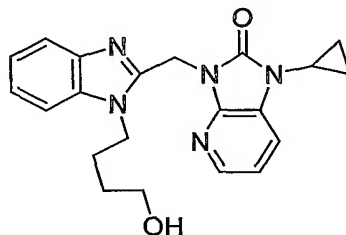
Example 154

- ^1H NMR (CD_3OD) δ 1.16-1.20 (m, 2 H), 1.21-1.27 (m, 2 H), 2.44-2.48 (m, 1 H),
15 2.51-2.56 (m, 1 H), 3.18-3.22 (m, 1 H), 3.32-3.34 (m, 1 H), 3.74-3.78 (m, 1 H),
4.73-4.78 (m, 1 H), 4.81-4.89 (m, 2 H), 6.01 (d, 2 H), 7.63-7.67 (m, 1 H), 7.68-
7.72 (m, 1 H), 7.79 (d, $J=8.2$ Hz, 1 H), 7.94 (d, $J=6.4$ Hz, 1 H), 8.02 (d, $J=8.3$ Hz,
1 H), 8.61 (d, $J=6.4$ Hz, 1 H), 8.96 (s, 1 H);
MS m/e 419 (MH^+).

Example 155

- 5 ^1H NMR (CDCl_3) δ 1.00-1.03 (m, 2 H), 1.08-1.12 (m, 2 H), 1.68-1.74 (m, 2 H), 1.84-1.90 (m, 2 H), 2.06 (s, 3 H), 3.47-3.51 (m, 2 H), 4.09 (t, $J=6.3$ Hz, 2 H), 4.46 (t, $J=7.5$ Hz, 2 H), 5.42 (s, 2 H), 6.99-7.01 (m, 1 H), 7.20-7.27 (m, 2 H), 7.33-7.37 (m, 2 H), 7.76 (d, $J=7.6$ Hz, 1 H), 8.06-8.07 (m, 1 H);
MS m/e 420 (MH^+).

10

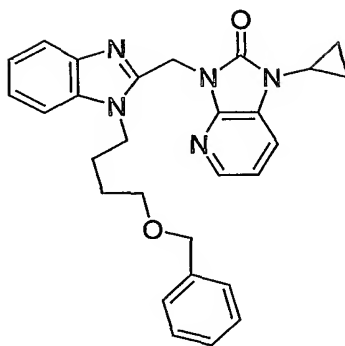
Example 156

- 15 Example 156 was prepared from Example 155 according to the same procedure described for Example 73.

- ^1H NMR (CD_3OD) δ 1.01-1.04 (m, 2 H), 1.13-1.68 (m, 2 H), 1.63-1.68 (m, 2 H), 1.94-2.01 (m, 2 H), 2.68 (s, 3 H), 3.01-3.04 (m, 1 H), 3.60 (t, $J=6.2$ Hz, 2 H), 4.69 (t, $J=7.9$ Hz, 2 H), 5.73 (s, 2 H), 7.19-7.22 (m, 1 H), 7.63-7.69 (m, 3 H), 7.74-7.76 (m, 1 H), 7.98 (d, $J=7.6$ Hz, 1 H), 8.03-8.04 (m, 1 H);
MS m/e 478 (MH^+);

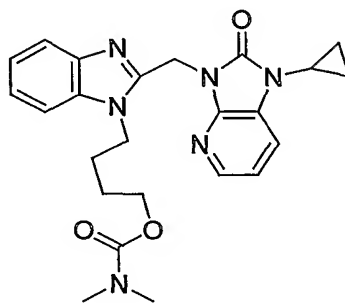
Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_2 \cdot \text{CH}_4\text{O}_3\text{S} \cdot 0.75 \text{H}_2\text{O}$: C, 54.21; H, 5.85; N, 14.22

Found: C, 54.25; H, 5.90; N, 14.38.

Example 157

- 5 ^1H NMR (CDCl_3) δ 0.98-1.01 (m, 2 H), 1.07-1.10 (m, 2 H), 1.65-1.71 (m, 2 H), 1.84-1.90 (m, 2 H), 2.86-2.90 (m, 1 H), 3.47-3.51 (m, 2 H), 4.43 (t, $J=7.6$ Hz, 2 H), 4.47 (s, 2 H), 5.37 (s, 2 H), 6.97-6.99 (m, 1 H), 7.18-7.33 (m, 9 H), 7.72-7.74 (m, 1 H), 8.03-8.06 (m, 1 H);
MS m/e 468 (MH^+).

10

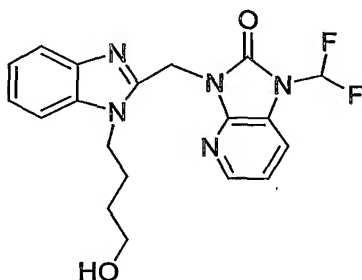
Example 158

- 15 To a suspension of Example **156** (52 mg, 0.14 mmol) and sodium hydride (6.6 mg, 0.16 mmol) in DMF (2 mL) was added N,N-dimethylcarbamoyl chloride (16.2 mg, 0.15 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 12 hours. The mixture was diluted with EtOAc and washed with water. The organic extracts were dried with MgSO_4 and evaporated. The residue
20 was purified by flash chromatography (gradient, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 40:1 to 20:1) to give 35 mg (56% yield) of Example **158** as a off-white solid.

^1H NMR (CDCl_3) δ 1.00-1.03 (m, 2 H), 1.08-1.12 (m, 2 H), 1.68-1.74 (m, 2 H), 1.84-1.90 (m, 2 H), 2.84 (s, 3 H), 2.90-2.93 (m, 4 H), 4.09 (t, $J=6.3$ Hz, 2 H), 4.46 (t, $J=7.5$ Hz, 2 H), 5.42 (s, 2 H), 6.99-7.01 (m, 1 H), 7.20-7.27 (m, 2 H), 7.33-7.37 (m, 2 H), 7.76 (d, $J=7.6$ Hz, 1 H), 8.06-8.07 (m, 1 H);

5 MS m/e 449 (MH^+).

Example 159



10

Example 159 was prepared via synthesis of the acetate intermediate according to the same procedure described for Example 72 followed immediately by deprotection of the alcohol according to the same procedure described for Example 73.

15

^1H NMR (d_6 -DMSO) δ 1.44-1.54 (m, 2 H), 1.77-1.86 (m, 2 H), 3.41 (t, $J = 6.3$ Hz, 2 H), 4.46 (t, $J = 7.2$ Hz, 2 H), 5.53 (s, 2 H), 7.21 (dd, $J = 5.3, 8.0$ Hz, 1 H), 7.28-7.40 (m, 2 H), 7.59 (d, $J = 7.8$ Hz, 1 H), 7.76 (d, $J = 7.8$ Hz, 2 H), 7.84 (t, $J = 57.6$ Hz, 1 H), 8.10 (d, $J = 4.8$ Hz, 1 H);

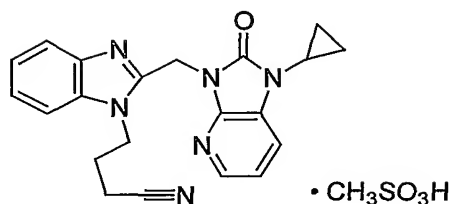
20 IR (KBr, cm^{-1}) 3275, 2941, 1751, 1623, 1606, 1466, 2503, 1031, 772, 746;

MS m/e 388 (MH^+);

Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{F}_2\text{N}_5\text{O}_2 \cdot 0.25 \text{H}_2\text{O}$: C, 58.23; H, 5.02; N, 17.87

Found: C, 58.42; H, 4.79; N, 17.64.

182

Example 160

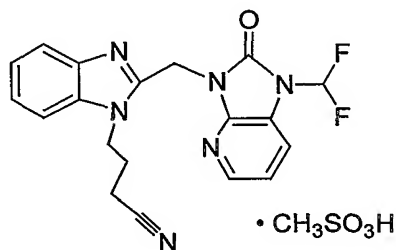
5 ¹H NMR (CD₃OD) δ 1.02-1.05 (m, 2 H), 1.11-1.17 (m, 2 H), 2.32-2.38 (m, 2 H), 2.68 (s, 3 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.01-3.05 (m, 1 H), 5.79 (s, 2 H), 7.20-7.22 (m, 1 H), 7.64-7.76 (m, 4 H), 7.99-8.05 (m, 2 H);

MS m/e 373 (MH⁺);

Anal. Calcd for C₁₉H₁₈N₈O•1.0 H₂O•1.0 CH₄SO₃: C, 54.31; H, 5.39; N, 17.27

10

Found: C, 54.58; H, 5.37; N, 17.37.

Example 161

15

¹H NMR (CD₃OD) δ 2.37-2.40 (m, 2 H), 2.68 (s, 3 H), 2.73 (t, J = 7.3 Hz, 2 H), 4.82 (t, J = 7.6 Hz, 2 H), 5.80 (s, 2 H), 7.26-7.28 (m, 1 H), 7.62 (t, J = 58.0 Hz, 1 H), 7.65-7.79 (m, 4 H), 8.00 (d, J = 8.3 Hz, 1 H), 8.17 (dd, J = 1.3, 5.3 Hz, 1 H);

IR (KBr, cm⁻¹) 3449, 3064, 2953, 1758, 1466, 1410, 1230, 1156, 1048, 771, 551;

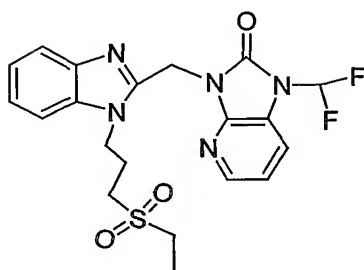
20

MS m/e 383 (MH⁺);

Anal. Calcd for C₁₉H₁₆F₂N₆O•0.5 H₂O•1.0 CH₃SO₃H:

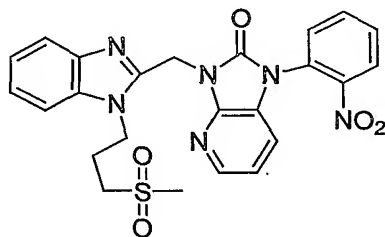
C, 49.28; H, 4.34; N, 17.24

Found: C, 49.36; H, 4.42; N, 16.95.

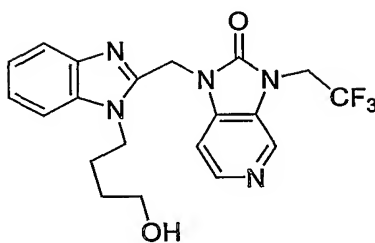
Example 162

- 5 ^1H NMR (CD_3OD) δ 1.35 (t, $J = 7.5$ Hz, 3 H), 2.50-2.57 (m, 2 H), 3.15 (q, $J = 7.5$ Hz, 2 H), 3.35 (t, $J = 7.2$ Hz, 2 H), 4.86 (t, $J = 7.2$ Hz, 2 H), 5.77 (s, 2 H), 7.24-7.27 (m, 1 H), 7.59-7.68 (m, 3 H), 7.62 (t, $J = 58.0$ Hz, 1 H), 7.71 (d, $J = 8.3$ Hz, 1 H), 7.78 (d, $J = 7.8$ Hz, 1 H), 7.98 (d, $J = 8.1$ Hz, 1 H), 8.16 (d, $J = 5.2$ Hz, 1 H); MS m/e 450 (MH^+).

10

Example 163

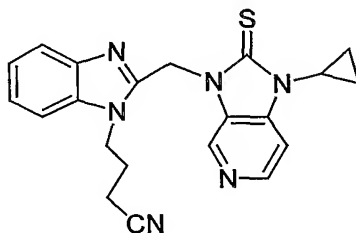
- 15 ^1H NMR ($\text{DMSO}-d_6$, 65°C) δ 2.81-2.34 (m, 2 H), 2.99 (s, 3 H), 3.28 (t, $J = 7.7$ Hz, 2 H), 4.57 (t, $J = 7.4$ Hz, 2 H), 5.50 (s, 2 H), 7.14-7.19 (m, 2 H), 7.25-7.27 (m, 1 H), 7.41 (d, $J = 8.0$ Hz, 1 H), 7.53 (d, $J = 7.9$ Hz, 1 H), 7.63 (d, $J = 8.1$ Hz, 1 H), 7.80-7.84 (m, 1 H), 7.91 (d, $J = 7.6$ Hz, 1 H), 7.98-8.02 (m, 1 H), 8.09 (d, $J = 5.0$ Hz, 1 H), 8.25-8.27 (m, 1 H);
- 20 MS m/e 507 (MH^+).

Example 164

5 Example 164 was prepared via synthesis of the acetate intermediate according to the same procedure described for Example 72 followed immediately by deprotection of the alcohol according to the same procedure described for Example 73.

10 ¹H NMR (CDCl₃) δ 1.60-1.65 (m, 2 H), 1.73-1.80 (m, 2 H), 3.64-3.70 (m, 2 H), 4.33 (t, J=8.0 Hz, 2 H), 4.53-4.60 (m, 2 H), 5.44 (s, 2 H), 7.24-7.37 (m, 3 H), 7.60 (d, J=5.3 Hz, 1 H), 7.77-7.81 (m, 1 H), 8.35-8.38 (m, 2 H); MS m/e 420 (MH⁺).

15

Example 165

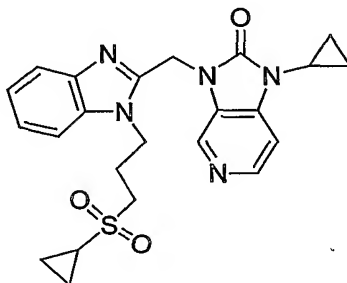
20 A mixture of Example 26 (100 mg, 0.27 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 130 mg, 0.32 mmol) in a mixture of toluene and dioxane (9:1 ratio, 10 mL) was heated in a sealed tube at 130 °C for 15 hours. The solvents were removed *in vacuo* and the residue was suspended in H₂O and extracted with CH₂Cl₂. The organic phase was washed with brine, dried over MgSO₄ and evaporated. The residue was purified by preparative TLC (5% MeOH in CH₂Cl₂), followed by

25

trituration from Et₂O to give 5 mg (5 % yield) of Example 165 as an off white solid.

¹H NMR (DMSO-d₆) δ 1.05-1.10 (m, 2 H), 1.21-1.25 (m, 2 H), 2.07-2.15 (m, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 3.23-3.26 (m, 1 H), 4.49 (t, J = 7.5 Hz, 2 H), 5.90 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.59 (d, J = 5.5 Hz, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 8.42 (d, J = 5.5 Hz, 1 H), 8.76 (s, 1 H);
MS m/e 389 (MH⁺).

10

Example 166

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as RSV infection. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally-administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 0.1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 0.1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage

for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the
5 severity of the particular condition, and the host undergoing therapy.

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial
10 virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at 1.5×10^4 cells/100 μ L/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μ L volume in medium
15 containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μ L at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was
20 aspirated from the cells and 100 μ L/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the
25 number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μ g/mL (corresponding to 10.2 μ M).

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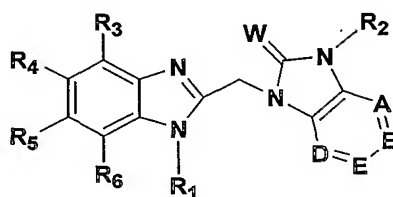
The antiviral activity of compounds, designated as EC₅₀, is presented as a concentration that produces 50% cell protection in the assay. The compounds

disclosed in this application show antiviral activity with EC₅₀s between 50 μ M and 0.001 μ M. Ribavirin has an EC₅₀ of 3 μ M.

CLAIMS

What is claimed is:

- 5 1. A compound having the Formula I, and pharmaceutically acceptable salts thereof,



Formula I

10

wherein:

W is O or S;

- 15 R_1 is $-(CR'R'')_n-X$;

X is H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR''', NR'R'', NR'COR'', NR'CONR''R''', NR'SO₂R'', NR'COOR'', COR', 20 CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', PO(OR')₂, aryl, heteroaryl or non-aromatic heterocycle;

m is 0-2; n is 2-6;

25

R_2 is

(i) H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl,

$-(CH_2)_t$ C₃₋₇ cycloalkyl, $-(CH_2)_t$ C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is

1-6;

5

(ii) $-(CR'R'')_n-Y$, wherein Y is CN, OR', OCONR'R", NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR'R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂; wherein

10 m is 0-2 and n' is 1-6;

(iii) $-(CR'R'')_n-C_6H_4-Z$, wherein the Z group may be in the ortho, meta or para position relative to the $-(CH_2)_n$ group; Z is CN, OR', OCONR'R", NO₂, NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR'R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂;

15

m is 0-2; n" is 0-6; or

(iv) $-(CR'R'')_{n'''}-heteroaryl$, wherein n''' is 0-6;

20

(v) $-(CR'R'')_{n'''}-non-aromatic\ heterocycle$, wherein n''' is 0-6;

R₃, R₄, R₅ and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkyl substituted with one to six of the same or different halogen atoms, OR', CN, COR', COOR', CONR'R", or NO₂;

25

A, B, E, D are each independently C-H, C-Q-, N, or N-O; provided at least one of A, B, E or D is not C-H or C-Q; wherein Q is halogen, C₁₋₃ alkyl or C₁₋₃ alkyl substituted with one to three of the same or different halogen atoms; and

30

R', R", R''' are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or

different halogen atoms; or R' and R'' taken together form a cyclic alkyl group having 3 to 7 carbon atoms; benzyl, or aryl;

- R''' is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl,
5 NR'R'', CR'NR''R''', aryl, heteroaryl, non-aromatic heterocycle; and

Non-aromatic heterocycle is a 3-7 membered non-aromatic ring containing at least one and up to 4 non-carbon atoms selected from the group consisting of O, S, N, and NR';

10

Aryl is phenyl, naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl;

Heteroaryl is a 4-7 membered aromatic ring which contains one to five heteroatoms independently selected from the group consisting of O, S, N or NR',

- 15 wherein said aromatic ring is optionally fused to group B';

B' is an aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl;

- 20 Aryl, B', said 4-7 membered aromatic ring, and said 3-7 membered non-aromatic ring may each independently contain one to five substituents which are each independently selected from R₇, R₈, R₉, R₁₀ or R₁₁; and

R₇, R₈, R₉, R₁₀ and R₁₁ are each independently

- 25 (i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; and

(ii) halogen, CN, NO₂, OR', NR'R'', COR', COOR', CONR'R'', OCOR', NR'COR'', SO_mR', SO₂NR'R'', PO(OR')₂.

2. The compound of claim 1 wherein heteroaryl is selected from the group
 5 consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl,
 10 benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, tetrazole and phenoxazinyl.

- 15 3. A compound of claim 2 wherein:

R₁ is -(CH₂)_n-X;

- X is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl,
 20 each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'', NR'R'', NR'COR'', NR'COOR'', COR', CR''NRR'', CR'NOR'', COOR', CONR'R'', SO_mR', aryl or heteroaryl;

- 25 m is 0-2; n is 2-4;

R₂ is

- (i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, -(CH₂)_t C₃₋₇ cycloalkyl, -(CH₂)_t C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is 1-6;
- (ii) -(CH₂)_n-Y, wherein Y is CN, OR', COR', COOR', CONR'R", SO_mR', SO₂NR'R", PO(OR')₂ wherein m is 0-2 and n' is 1-6; or
- (iii) -(CH₂)_n"-C₆H₄-Z, wherein the Z group may be in the ortho, meta or para position relative to the -(CH₂)_n" group; Z is CN, OR', COR' or SO_mR'; m is 0-2; n" is 0-3;
- R₃, R₄, R₅, and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, optionally substituted with one to six of the same or different halogen atoms; and
- A, B, E, D are each independently C-H or N; provided at least one of A, B, E or D is not C-H.
4. A compound of claim 2 wherein:
- R₃, R₄, R₅ and R₆ are each H;
- A, B and D are each C-H; and
- E is N.
5. A compound of claim 2 wherein:
- R₃, R₄, R₅ and R₆ are each H;
- A, B and E are each C-H; and


D is N.

6. A method for treating mammals infected with RSV, and in need thereof,
which comprises administering to said mammal a therapeutically effective amount
5 of a compound having the Formula I, and pharmaceutically acceptable salts
thereof, as claimed in any one of claims 1-5.
7. A pharmaceutical composition which comprises a therapeutically effective
amount of an anti-RSV compound having Formula I, and pharmaceutically
10 acceptable salts thereof, as claimed in any one of claims 1-5, and a
pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/14775

A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : A61K 31/495, 31/50, 31/52, 31/44; A61P 31/12; C07D 471/02, 473/30, 487/02		
US CL : 514/248, 249, 262, 303; 544/236, 265, 276, 350; 546/118		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
U.S. : 514/248, 249, 262, 303; 544/236, 265, 276, 350; 546/118		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CRANK et al., Photochemistry of Heterocycles. III* Photolysis of Various 2-Substituted Benzimidazoles, Australian Journal of Chemistry, 1982, Vol. 35, No. 4, pages 775-784, especially example 5, page 777.	1-7
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
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21 September 2001 (21.09.2001)		25 OCT 2001
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